The impact of maternal-fetal omalizumab transfer on peanut-specific responses in an ex vivo placental perfusion model

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May 12, 2022

\textbf{Article Type:} Letter to the Editor  
\textbf{Title:} The impact of maternal-fetal omalizumab transfer on peanut-specific responses in an \textit{ex vivo} placental perfusion model  
\textbf{To the Editor:}

The transport of maternal IgG to the fetus is mediated by neonatal Fc receptors (FcRn) expressed on the placenta, which provides passive immunity \textit{in utero}. Humanized monoclonal antibodies such as omalizumab bind to FcRn and are transferred to the fetus. Recently, Bundhoo et al. provided \textit{in vitro} data of FcRn-mediated anti-IgE IgG/IgE immune complexes, suggesting a mechanism for IgE transfer across the placenta to the fetus. As IgG bound allergens are also known to cross the placenta, it is important to understand the impact of omalizumab, one of the most frequently prescribed monoclonal antibodies to treat severe asthma in reproductive age.

We report the use of a state-of-the-art \textit{ex vivo} human placental perfusion system to investigate the impact of omalizumab on the transport of peanut allergen and IgE across the placenta (Figure 1A). We compared the transport of maternal IgG to the fetus is mediated by neonatal Fc receptors (FcRn) expressed on the placenta, which provides passive immunity \textit{in utero}. Humanized monoclonal antibodies such as omalizumab bind to FcRn and are transferred to the fetus. Recently, Bundhoo et al. provided \textit{in vitro} data of FcRn-mediated anti-IgE IgG/IgE immune complexes, suggesting a mechanism for IgE transfer across the placenta to the fetus. As IgG bound allergens are also known to cross the placenta, it is important to understand the impact of omalizumab, one of the most frequently prescribed monoclonal antibodies to treat severe asthma in reproductive age.

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To compare the degree to which FcRn might facilitate the transfer of allergen-IgG complexes across the placenta, we examined Ara h 2 transfer in the presence (PE/PA) or absence (PE) of plasma from peanut-allergic individuals, with (PE/PA/Oma) and without omalizumab (Figure 2A). PE/PA crossed the placenta with a moderate rise of Ara h 2 levels at the fetal side after 120 min, comparable to PE alone (1.03 ng/mL). Extending the perfusion time to 240 min resulted in a near two-fold increase (3.82 ng/mL) of PE via
PE/PA/Oma vs. PE/PA (1.97 ng/mL). The transferred peanut proteins were fully capable of crosslinking IgE as confirmed via BAT (Figure 2B). The higher degree of basophil activation matched the extent of Ara h 2 transfer. We confirmed that perfusion medium alone did not activate basophils (Figure S1). Furthermore, evidence for omalizumab-driven IgE transfer resulting in free IgE with possible functionality was assessed via incubation of stripped basophils with perfusates. We could not find evidence for IgE binding to basophils from these eluates (Figure S2).

In conclusion, functional peanut allergen is actively transported across the human placenta and this process may be enhanced by omalizumab. Active transfer of free IgE to the fetal side due to FcRn mediated complex formation was not observed. Further studies are needed to better understand how allergen-antibody complexes affect allergen-specific priming in the fetus with and without biological usage during pregnancy.

References

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Conflicts of Interest: AK, BH, JSL, BP, KS, and CW have nothing to disclose. ZS holds advisory board roles for Nutricia/Danone, Aimmune and Sanofi. TE reports to act as local PI for company sponsored trials by DBV and sub-investigator for Regeneron, holds grants from Innovation Fund Denmark, CIHR outside the submitted work. He is Co-Investigator or scientific lead in three investigator-initiated oral immunotherapy
trials supported by the Food Allergy and Anaphylaxis Program SickKids and serves as an associate editor for Allergy. He/his lab received unconditional/in-kind contributions from Macro Array Diagnostics and an unrestricted grant from ALK. He holds advisory board roles for ALK, Nutricia/Danone and Aimmune.

**Financial support:** This work was supported by The Hospital for Sick Children (Food Allergy and Anaphylaxis Program, start-up funds by the SickKids Research Institute and the Department of Pediatrics, Restracomp Graduate Scholarship to AK), and an Ontario Graduate Scholarship from the Province of Ontario to AK.

**Statement of Author Contribution:** AK, BH, JSL, and KS contributed to data acquisition. TE, BH and CW contributed to experimental designs. AK, BH, JSL, BF, KS, CW, ZS, and TE contributed to data interpretation and preparation of the manuscript. The final version of the manuscript was approved by all authors.

**Keywords:** omalizumab, placental transport, *ex vivo* placental perfusion system, peanut allergy, basophil activation test

**Abbreviations:** FcRn; neonatal Fc receptors; BAT, basophil activation test; Oma, omalizumab

**Word Count:** 529

**Figure Legends:**

**Figure 1.** Transfer of Omalizumab and Peanut protein across the placental barrier.

(A) In the human placental *ex vivo* model sample in-flow (artery) and out-flow (vein) are recorded to and from the placental tissue. (B) Omalizumab and (C) peanut extract transfer kinetics as percent change from maternal artery to fetal vein detected via ELISA.

**Figure 2.** Placental peanut allergen transfer in the context of plasma from allergic individual and omalizumab. (A) Ara h 2 concentrations (ng/mL) in fetal vein and artery samples were determined by ELISA in PE alone (dashed line, 1.03 ng/mL) and PE/PA compared to PE/PA/Oma experiments. (B) Basophil activation tests were conducted by flow cytometry to assess the functionality of transferred allergen. Activation levels are expressed as %CD63+ basophils in PE, PE/PA and PE/PA/Oma experiments.
PE Perfusate

- Maternal Artery
- Fetal Vein

Time (min)