Placental Transfer of Immunosuppressive Biologics: Current Clinical Pharmacology Landscape

Edwin Lam, PharmD

Johnson & Johnson Innovative Medicines Maternal-Fetal Immunology Clinical Pharmacology Lead

Johnson&Johnson

Innovation

Transplacental passage of immunoglobulins is mediated by the neonatal Fc receptor (FcRn)

FcRn, but not FcyRs, drives maternal-fetal

transplacental transport of human IgG antibodies Sara Borghi^{a,1}^(a), Stylianos Bournazos^{a,1}, Natalie K. Thulin^b, Chao Li⁵, Anna Gajewski^d, Robert W. Sherwood^{*},

However, no association between placental FcRn expression and maternal-to-fetal transfer of IgG



IgG1 preferentially transported; cord to maternal blood ratio expected to be ~1.5. In utero transfer of therapeutic mAbs postulated to be facilitated by placental FcRn while maternal FcRn is responsible for maintaining IgG half-life (including biologics)

J&J

Clements T et al. Front Immunol. 2020 Sep 11;11:1920.

Maternal-fetal IgG transport increases with gestational age

Transport increases throughout gestation exceeding maternal IgG towards term as evidenced by the fetal:maternal (F:M) IgG ratio



Given that most biologics are engineered with various IgG subtype constant regions, what is the current evidence surrounding in utero exposure for immunosuppressive monoclonals?

Evidence suggests modest to lower serum monoclonal antibody (mAb) exposure during pregnancy

Is transplacental crossing of immunosuppressive biologics similar to IgG?



Most biologics with immunosuppressive properties are IgG1

Class	Drug	mAb Structure	ructure Evidence of transfer (F:M Ratio)		
Anti-TNFa	Golimumab	lgG1	1.21 (n = 1)	Case	
	Certolizumab-PEG	lgG1 (PEGlayted Fc)	<1.0	Prospective, Observational	
	Infliximab	IgG1 (chimeric)	1.97 (1.50 – 2.43)		
	Adalimumab	lgG1	1.21 (0.94 – 1.49)		
Anti-Cytokine	Ustekinumab	lgG1	1.70 (1.2 – 2.5)		
Anti-Integrin	Vedolizumab	lgG1	0.70 (0.60 – 0.90)		
	Natalizumab	lgG4	1.63 (0.4 – 4.44)	Case	
Anti-Complement	Eculizumab	lgG2/4	Detectable cord blood		
Anti-B Cell	Belimumab	lgG1	1.49 (n = 1)		

F:M ratio often used as surrogate of in utero exposure throughout gestation, however limitations exist given various sampling points along the concentration-time curve

Julsgaard M et al. Gastroenterology. 2016 Jul;151(1):110-9. Prentice R et al. Clin Gastroenterol Hepatol. 2024 Mar 15:S1542-3565(24)00252-0. Benoit L et al. Crohns Colitis. 2019 Apr 26;13(5):669-670. Bitter H et al. Ann Rheum Dis. 2023 Apr;82(4):577-579. Haghikia A. et al. JAMA Neurol. 2014 Jul 1;71(7):891-5. Kelly RJ et al. N Engl J Med. 2015 Sep 10;373(11):1032-9.

Informative clinical PK data has mostly been observed with a limited number of immunosuppressive biologics

These include anti-TNFa, integrin, & cytokine monoclonals which have been used to contextualize most biologics with immunosuppressive activity

- Mostly maternal-fetal (cord) paired blood samples to estimate in utero exposure
 - Estimate the F:M ratio; gauge the magnitude of placental crossing near term
 - Estimate time to clearance using population PK/PD approaches
- Post-natal infant collection allows estimation of the extent of persistence in the exposed infant
 - Sampling beyond the birth collection in infants (e.g. 4, 8, 12 weeks, etc.) are informative
 - Address questions such as timing of live vaccine administration or exposure-response relationships for developmental or infection AEs
- The relationship between exposure and target engagement/receptor occupancy in the infant is limited
 - Mechanistic interpretation between exposure in the infant and downstream effector impact is limited
 - Limited to clinical observations for developmental and infection outcomes

6

Exposure and time to clearance of drug generally correlates with duration since last maternal dose

Time to undetectable levels generally depends on timing of previous dose at delivery



Drug	F:M Ratio
Vedolizumab	0.7
Ustekinumab	1.70
Infliximab	1.97
Adalimumab	1.21

Julsgaard M et al. Gastroenterology. 2016 Jul;151(1):110-9 Flanagan PR et al. Clin Gastroenterol Hepatol. 2024 Mar 15:S1542-3565(24)00252-0.

Study designs enabling birth and postnatal blood collection can inform clinical decisions and estimate infant clearance

The use of population PK modeling have been implemented to address questions such as time to undetectable concentrations enabling timing of live vaccination



Liu Z et al. J Crohns Colitis. 2022 Dec 5;16(12):1835-1844. Wieringa JW et al. J Crohns Colitis. 2024 Apr 23;18(4):506-515.

Mechanistic and compound considerations to guide study designs

IgG Fc-free region are not expected to undergo FcRn mediated placental transfer which can minimize the number of infant sampling



Studies evaluating in utero exposure of immunosuppressive biologics are limited to birth collection

Prospective cord blood collection most often collected at delivery to estimate maternal-fetal exposure in utero



Fetal and Neonatal Drug Exposure Following Nipocalimab Treatment in Pregnant Individuals at Risk of Early-onset Severe Hemolytic Disease of the Fetus and Newborn (EOS-HDFN)

0, PhD"; Jer Zhou, PhD"; Yuan Kong, PhDF; Anin, MRRS; Waheeda Sicah, MS;	Sphrasen & Johnson Trinsvative Medicine, 1054, Tohnson & Johnson Trinsvative Wedicine, a divesses of gamsan Pharmaceutica Wd. Biorna, Belgium.					KEY TAKEAWAY			
(McAndo Ropo Calla, MD)							<i>.</i>	Overall duration of fetal and neonat drug exposure was limited and generally below the level expected	
NDPh) is a care, the diversity candidan that, is about have a stack that and tood calls' carbout have a stack that and tood calls' bidly and or calls, with aveat that nearbing more pilots and probably designed to delectually general pilots and	RESULTS Participants - Of the 13 programote, 12 resulted in live births and 1 resulted in fisal loss due to intrauterine transfusion complications at - 22 th mests GA Peta plasmacekinetics						for FChn RO following nipocalimab dosing between 14 and 35 weeks G in pregnant participants at high risk for EOS-HDFN		
ter and the sole lgG schage receptor entit laG manufact and manufactureness of train	 A total of 5 pregnancies required consocentesis, or which 5 has available cold blood samples 						CON	CLUSIONS.	
gG allownibody concentrations autibody stander to the fatus and lower open-label insi (UNET): ClevicalTratis.gov of or reduced the risk of fatal avenue and	where we have a set of the set of							Undetectable or negligible levels of nipocalimab were observed in available fetal and neonatal samples and were well below the effective concentration	
nd bassen/hean-peor/entres, with no cansaul IN-55% before taxedines in programster, at high with in transmitmentant with heigh to understand									
ts association with the observed labely and like	Intere was no detectable pharmacosynamic effect or inpocalimatio on the fetus/neonate at posthatal week 4 Meanated absense Academics							for >90% FCKn RO, indicating that drug	
inable fistator and resonates delivered by	• At birth, nipocalimations was detected in 1 of 11 available neonatal samples, with a concentration of 0.7 µg/mL (7 days after the last dose in a materian and nativica and from the 30.45 molec dose error who met the primary endovier. Table 1.							dosing between 14 and 35 weeks GA	
outly) was administrated to program	 The occupied FCRI measured at birth for this neonate was 15.8%, indicating an absence of full FCRI RO The igG level at birth for this neonate was 162 mg/d, which was within the range 02.306 mg/dJ, besived in other neonates delivered by maternal participants what also me the primary implement to that An other decisit imposition at birth 							The observation of low neonatal IgG le is in line with the expected mechanism of action of nipocalimab inhibition of maternal transplacental IgG transfer	
in 14 and 10 weeks 104, with an expected	 At postnatal Week 4, nipocalimab was undetectable in all available 	 At postnatał Week 4, nipocalimab was undetectable in all available neonatal samples (Table 1) 							
n programsy 104 5-14 weeks) who had a finitery a anti-Dram - K also mitbody tawn, and an etal DNA genetyping in the cument programsy	 Fetal IgG concentrations In 5 samples available at first intrauterine transfusion, the 	TABLE 1: Serum nipocalimab concentrations in neonates at birth and postnatal Week 4 Maternal nipocalimab dose group					Further data on fetal/neonatal exposure to nipocalimab will be collected in the pivotal phase 3 study in severe HDFN (ClinicalTrials.gov Identifier: NCT059125)		
fallen-ap	fetal to maternal IgG concentration ratios were 48(157, 43:196, 46:177, 43:197, and 43:157, mg/dL, which were below the values expected in typical pregnances ^{1,3} - One maternal IgG concentration (-64 mg/dL) was actually a fetal confocenties sample that was mislabeled by the								
anight deserts anight hady seaght deserts			30 mg/kg BLW	30-45 mg/kg BLW	45 mg/kg BLW	45 mg/kg TAW			
f or Ad anagering sales()	Neonatal IIG concentrations	At birth, N	(Z)	2.	- 4	3	ACKNO	WLEDGMENTS	
A Descention of the Approximation Manuscript Print, Descention of Print,	 At birth, the median (range) neonatal serum IgG was 181 (90-040) mg/dL 	Median (range).	0.028	0.35(0-0.7)	om	0.001	this standy of taggerst was and was for	The body were sponsored by proceed workers to Committee and a strategy community of proceedings of the strategy of the strategy and were known by preserve factor Services, LLC.	
10 27 24 M	 IgG values were below the normal range at birth (lower limit of normal: 636 mg/dL^p in all neonates delivered by maternal 	hburr,					DISCL FL.PG. 22 st presson	DSURES X. LEL. N.T. LIA. W.Y. YSLR, AM, W. JW MC. RRC. MMH, and BV are employ & prevant Presentine Medicine and may head stack/stacks agreeme into	
aliante di merupikat i 17 menerumkan	participants treated with nipocalimab within 2 to 3 weeks of delivery and supplemented with intravenous immunoglobulin	At postnatal Week 4 N	3	0	4	3	jademaan da j	denne.	

GA Week 31 cordocentesis collection F:M ratio < 0.1 (0.04 : 522 ug/mL)

Opportunistic cord blood collection for clinically indicated procedures (e.g. cordocentesis) throughout gestation is informative

Studies remain limited but the body of evidence is growing

Most of the clinical evidence generated are limited to post-marketing prospective PK studies; seldom observations from clinical development programs pre-approval

- Placental transfer of monoclonal antibodies are mediated by FcRn
 - IgG subtype; IgG1 > IgG3>IgG2=IgG4
 - Most biologics with IgG1 constant region have F:M ratios similar to native IgG1; considerations for fusion proteins with nonnative IgG Fc portion (e.g. PEGylated)
- Most clinical pharmacology data are collected from prospective post-marketing studies
 - Time to clearance dependent on the time since last maternal dose and subsequent in utero and postnatal infant exposure
 - Limitations can arise with interpreting F:M ratios; most clinical experience coming from anti-TNFs
 - Study designs should consider maternal-neonate pair samples collected at birth but also longitudinal postnatal sampling; use of population PK/PD modeling to address time to clearance
 - Use of opportunistic samples as part of clinical care during gestation (i.e. at 2nd/3rd trimester) to evaluate drug levels in utero
- Target engagement/exposure threshold
 - Limited evaluations accounting the relationship between infant exposure of immunosuppressive biologics, target engagement and effect and/or outcome

J&J

11