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Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): Consequences for FcRn-mediated *in vitro* transcytosis and *ex vivo* human placental transfer

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ABSTRACT

Antibodies to tumor necrosis factor (anti-TNF) are used to treat inflammatory diseases, which often affect women of childbearing age. The active transfer of these antibodies across the placenta by binding of the Fc-region to the neonatal Fc receptor (FcRn) may result in adverse fetal or neonatal effects. In contrast to other anti-TNFs, certolizumab pegol lacks an Fc-region. The objective of this study was to determine whether the structure of certolizumab pegol limits active placental transfer.

Binding affinities of certolizumab pegol, infliximab, adalimumab and etanercept to human FcRn and FcRn-mediated transcytosis were determined using *in vitro* assays. Human placentas were perfused *ex vivo* to measure transfer of certolizumab pegol and positive control anti-D IgG from the maternal to fetal circulation.

FcRn binding affinity (K_D) was 132 nM, 225 nM and 1500 nM for infliximab, adalimumab and etanercept, respectively. There was no measurable certolizumab pegol binding affinity, similar to that of the negative control. FcRn-mediated transcytosis across a cell layer (mean ± SD; n = 3) was 249.6 ± 25.0 (infliximab), 159.0 ± 20.2 (adalimumab) and 81.3 ± 13.1 ng/mL (etanercept). Certolizumab pegol transcytosis (3.2 ± 3.4 ng/mL) was less than the negative control antibody (5.9 ± 4.6 ng/mL). No measurable transfer of certolizumab pegol from the maternal to the fetal circulation was observed in 5 out of 6 placentas that demonstrated positive-control IgG transport in the *ex vivo* perfusion model.

Together these results support the hypothesis that the unique structure of certolizumab pegol limits its transfer through the placenta to the fetus and may be responsible for previously reported differences in transfer of other anti-TNFs from mother to fetus.

1. Introduction

Tumor necrosis factor (TNF) alpha is an important cytokine in a number of diseases with a significant inflammatory component, including Crohn's disease (CD), rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) (Wiedmann et al., 2009). Biologic anti-TNF medications, including infliximab (IFX), adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab are frequently used for the treatment of such diseases.

Inflammatory diseases often affect women of reproductive age, and the risk of adverse pregnancy outcomes correlates with disease activity (Morales et al., 2000; Bush et al., 2004; Norgard et al., 2007; De Man et al., 2009). There is a need for adequate disease control during pregnancy (Ostensen and Forger, 2009; Mahadevan et al., 2011; Ng and Mahadevan, 2013), which has raised concern over the safety of biologic agents for pregnant and breast-feeding women. Current evidence from human studies suggests these agents do not pose a significant clinical risk to conception or early pregnancy (Ali et al., 2010; Fischer-Betz and Schneider, 2010, Mahadevan et al., 2012) or increase the risk of adverse outcomes (Raja et al., 2012;

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Marchioni and Lichtenstein, 2013). However, these reports advise to discontinue treatment in the third trimester to limit placental transfer; while such statements are cautionary through a lack of investigative knowledge, this conclusion is reflected in a number of treatment guidelines (Ostensen and Forger, 2009; Mahadevan et al., 2011; Ng and Mahadevan, 2013; Flint et al., 2016).

CZP has a unique structure compared to the other approved anti-TNF therapies, which may influence fetal exposure during pregnancy. It is a monovalent Fab' fragment of a humanized monoclonal attached to a polyethylene glycol (PEG) chain, which consequently lacks an Fc-region (Fig. 1) (Bourne et al., 2008; Rivkin, 2009). In contrast, the monoclonal antibodies IFX and ADA, and the TNF receptor-IgG Fc fusion protein ETA all possess an IgG1 Fc-region (Fig. 1). Binding of the IgG Fc-region to the neonatal Fc receptor (FcRn) plays an important role in regulating IgG homeostasis by protecting antibodies from degradation (Junghans and Anderson, 1996; Ghetie et al., 1997). In contrast, the plasma half-life of CZP is prolonged by the presence of a PEG moiety (Nesbitt et al., 2007). The IgG Fc-domain is also involved in the active transport of antibodies across the placenta, from maternal to fetal circulation, which is mediated by binding to FcRn (Roberts et al., 1990; Simister and Story, 1997; Saji et al., 1999). Thus, the presence or absence of an Fc-region would be expected to influence binding of biologics to FcRn and affect their active transport across the placenta.

The objective of this study was to determine whether the unique structure of CZP limits its active placental transfer.

2. Materials and methods

2.1. Therapeutic and control reagents

Infliximab (Tanabe Pharmaceutical, Osaka, Japan), adalimumab (Abbvie, Baar, Switzerland) and etanercept (Takeda Pharmaceutical, Osaka, Japan) were all purchased from European distributors. CZP, a control non-PEGylated CZP Fab' (control used in the FcRn binding assay) and P146 antibody (negative control used in the FcRn transcytosis assay) were supplied by UCB Pharma. The P146 negative control antibody was a whole IgG, with specificity to hapten 2,4-dinitrophenol (James and Tawfik, 2003), modified to prevent FcRn binding by mutation of three residues (I253A, H310A, H435A) within the Fc region identified as necessary for binding to FcRn (Roopenian and Akilesh, 2007). A polyclonal human anti-D IgG (supplied under agreement by CSL Behring), known to undergo materno-fetal transfer in the *ex vivo* placental transfer model (Urbaniak et al., 1997), was used as a positive control.

2.2. In vitro *human FcRn binding assay and quantification*

A label-free surface plasmon resonance-based assay (Biacore™, GE Healthcare UK) was used to determine the kinetics (on and off rates) and affinity (binding strength) of the interaction between the anti-TNFs and human FcRn. Binding of a non-PEGylated CZP Fab' was also assessed to determine whether PEGylation affected binding of the CZP Fab' to FcRn.

Human FcRn extracellular domain (IgG Fc-binding domain) was expressed in CHO cells transiently transfected with human FcRn alpha chain and beta 2-microglobulin (B_2M). The FcRn-B_2M heterodimer was prepared by affinity chromatography on a column of human IgG. The human FcRn extracellular domain was immobilized on the test chip by amine coupling to a level of 267 RU (response units). Samples were passed over the FcRn-coated chip (30 μL/min) in running buffer (0.02 M phosphate/0.15 M sodium chloride, pH 6.0/0.05% v/v polysorbate P20) for 5 min at a range of concentrations (0 nM, 21 nM, 42 nM, 84 nM, 168 nM, 335 nM and 670 nM) to determine the binding on-rate; pH 6 buffer was used to allow optimum binding. The FcRn binding model represents the intracellular environment and endosomal internalisation of IgG bound to the extracelluar FcR domain, which is known to be optimal at pH 6 and inactive at physiological pH (Chaudhury et al., 2003). The off-rate was followed for a further 5 min by running buffer alone over the chip. A zero control sensorgram was run every second cycle in order to account for baseline drift and bulk buffer effects; a total of 30 such controls were tested and all produced overlying sensorgrams close to baseline. The chip surface was regenerated between cycles using 3 × 80 s pulses of regeneration buffer (200 nM sodium chloride/100 mM TRIS, pH 8.0). Data were normalized by subtracting blank flow cell data and mean zero control cycle data. The average dissociation constant (K_D) for each compound was calculated from a global fit of association and dissociation kinetics measured over six concentrations (12 replicate experiments).

2.3. In vitro *human FcRn transcytosis assay and quantification*

Madin Darby Canine Kidney (MDCK-II) cells transfected with human FcRn and B_2M (Claypool et al., 2002) were cultured in minimal essential medium (MEM) supplemented with 10% v/v fetal bovine serum (FBS), 2 mM L-glutamine, 1% w/v non-essential amino acids, and 1% w/v sodium pyruvate (Invitrogen) at 37 °C/5% CO_2. The cells were cultured for 3 days in a 24-well transwell plate (BD Falcon), until an intact monolayer was formed, confirmed by measuring trans-epithelial resistances, which were at least 150 Ωcm^2 (Claypool et al., 2002).

The cells were washed with pH 7.2 Hanks' balanced salt solution (HBSS; Invitrogen), and biotinylated anti-TNFs (biotinylated using a kit from Roche) were added to the apical surface in HBSS pH 5.9 with 1% v/v bovine serum albumin (BSA) (pH adjusted with 10 mM 4-morpholineethanesulfonic acid [MES]) at 10 μg/mL. HBSS pH 7.2 with 1% v/v BSA (buffered with 10 mM HEPES) was added to the basolateral side. The use of 1% v/v BSA in the apical and basolateral surfaces was consistent with the methods described in the literature (Claypool et al., 2004). Anti-TNF concentration was quantified in the basolateral supernatant after 4 h' incubation at 37 °C. The 4-h sampling time was optimal for the assay to establish the maximum signal from the transcytosis assay without interfering with the integrity of the monolayer and was validated for specific FcRn-dependent transport with the P146 control (FcRn binding abolished) antibody in all assays. The amount of each anti-TNF transcytosed was measured using a meso scale discovery (MSD) electrochemiluminescent assay. The biotinylated anti-TNFs were captured on an MSD plate with an anti-human IgG antibody (Jackson Labs), then detected with a streptavidin sulpho-tag reagent (MSD). The electrochemiluminescent signal was determined using an MSD Sector Imager 6000 plate reader. Levels of each test anti-TNF were determined by comparison to a standard curve for each corresponding anti-TNF tested. Average (arithmetic mean) amount of anti-TNF transcytosed and the standard deviation (SD), were calculated for each anti-TNF from 3 replicate experiments.

2.4. Ex vivo *placental transfer model*

The collection of human placentas was subject to North of Scotland Research (NORES) Ethical Committee (Ethics Reference 09/S0801/006) and National Health Service (NHS) Grampian Research and Development Office approval and was audited (June 2010).

Freshly delivered placentas from elective caesarean sections were used after obtaining patients' written informed consent. Placental perfusion was carried out according to published methods (Duncan et al., 1995), previously validated for assessing IgG materno-fetal antibody transport (Armstrong-Fisher et al., 1997). Briefly, a placental lobule was cannulated from fetal and maternal

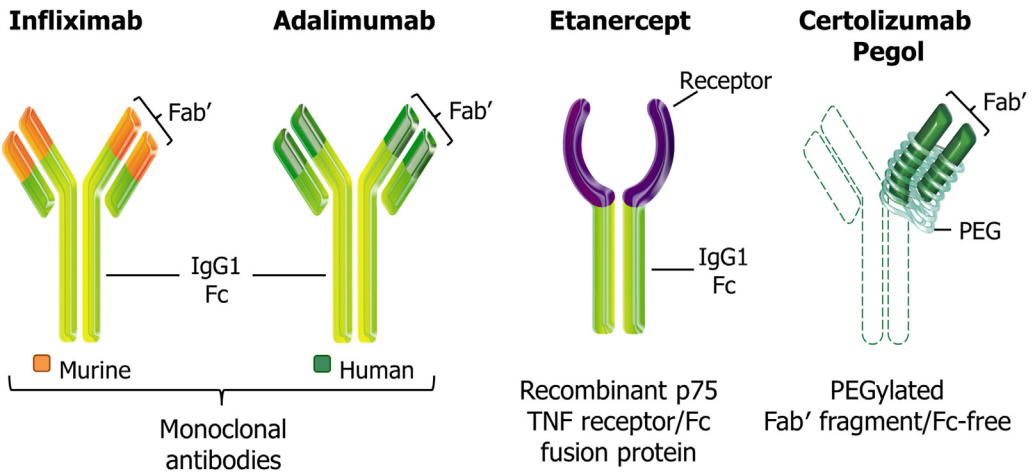

Fig. 1. Diagrammatic representations of the comparative structures of infliximab, adalimumab, etanercept and certolizumab pegol (CZP).
CZP has a unique structure compared to the other approved anti-TNF therapies, comprising of a monovalent Fab' fragment of a humanized monoclonal attached to a polyethylene glycol (PEG) chain, which consequently lacks an Fc-region.
Diagram adapted from Weir et al. (2006).

aspects, circulations were established, and the lobule was perfused for ≥30 min under 'open circuit' conditions at 37 °C to wash out erythrocytes and protein with RPMI-1640 media (Invitrogen) (fetal flow rate: ~6 mL/min; maternal flow rate: ~20 mL/min). Isolated lobules weighed, on average, 39.0 g; placental viability was confirmed by oxygen consumption. The 'fetal' circulation contained 95% N_2 and 5% CO_2, whereas the 'maternal' circulation contained 95% O_2 and 5% CO_2. Once circulation was established, the circuit was closed (ie. both circuits were in closed circuit perfusion). Subsequently, CZP (200 μg/mL) and positive control polyclonal anti-D IgG (30 μg/mL) were added simultaneously to 200 mL of perfusate (RPMI-1640 media, dextran and antibiotics) in the maternal circulation. The fetal perfusate consisted of 200 mL of perfusate with 0.363 g BSA added to provide what would be the normal protein content in the fetal placental circulation. Experiments were conducted for at least 4 h, with total perfusion time dependent on maintenance of tissue integrity, allowing re-circulation of antibodies through the placenta. The integrity of placental tissue was checked throughout perfusion by visual inspection, measurement of maternal and fetal reservoir volumes, and overall fetal return (mL/h × number of hours of perfusion, adjusted for fetal volume loss and expressed as a percentage), with a range of 84–97% fetal return.

Three 1 mL perfusate samples were collected from the maternal and fetal reservoirs at hourly intervals for up to 6 h. Samples were centrifuged (15,521*g*, 10 min) to remove cellular debris and stored at −40 °C. Triplicate samples at each time point were used for different measurements (*e.g.* anti-D or CZP quantification) and were not pooled for analysis.

2.5. Ex vivo *placental transfer model: quantification of CZP*

CZP in *ex vivo* placental perfusates was determined using an enzyme-linked immunosorbent assay (ELISA) (developed by UCB Pharma). The ELISA method lower limit of quantification was 0.41 μg CZP/mL perfusate. Perfusate samples were incubated for 1 h with immobilized human TNF alpha on 96-well plates. After washing, peroxidase-conjugated goat anti-human kappa light chain (which binds to CZP; MP Biomedicals) was added, and the plates were incubated for 30 min at room temperature (19–22 °C). Tetramethylbenzidine substrate solution was added after washing and the reaction stopped after 15 min. Absorbance was measured at 450 nm (with subtraction at 630 nm to eliminate background absorbance). Data were analyzed using Watson LIMS version 7.2 software (Thermo Scientific).

2.6. Ex vivo *placental transfer model: quantification of anti-D IgG*

Anti-D IgG concentrations were determined using a calibrated flow cytometric immunoassay with rhesus blood group D antigen (RhD)-positive red blood cells (RBCs). The lower limit of quantification of anti-D IgG was 0.008 μg/mL.

RBCs expressing RhD antigen were diluted to give a final concentration of 100×10^6 cells/mL. A standard curve was prepared using doubling dilutions of stock anti-D IgG between 1000 ng/mL and 0.06 ng/mL. Aliquots of RBCs were added to the respective anti-D IgG dilutions and incubated for 1 h at 37 °C. Cells were washed three times in phosphate buffered saline (PBS), then incubated in the dark for 20 min with a FITC conjugated-Fab' fragment of goat anti-human IgG (Fab′-FITC, ICN Pharmaceuticals/Valeant Pharmaceuticals) secondary antibody. Finally, RBCs were washed three times and then resuspended in PBS for anti-D IgG quantification by flow cytometry (Epics XL-MCL flow cytometer; Beckman Coulter). Mean channel fluorescence (MCF) values for each dilution were obtained, and a standard curve was plotted. Placental perfusion samples were processed as described above; fetal samples were used undiluted and maternal samples were diluted 1/100 in PBS. MCF values for all samples at each time point of closed-circuit perfusion were obtained. Concentration of anti-D IgG in each sample was calculated using the standard curve equation ($y = mx + c$). Final anti-D IgG concentrations were calculated and corrected for their dilution factor.

2.7. *Calculation of* ex-vivo *placental transfer*

Materno-fetal transfer of CZP and anti-D IgG was calculated as the transfer fraction (Tf%): Tf% = [IgG]f × 100/[IgG]m, where [IgG]f and [IgG]m = concentration of total anti-D IgG/CZP in the fetal (f) and maternal (m) circuits, respectively.

3. Results

3.1. In vitro *binding of anti-TNFs to human FcRn*

High binding affinities for FcRn were found with the monoclonal antibodies IFX and ADA (Table 1; Fig. 2A and B), which were

Table 1
Binding affinity of anti-TNFs for human FcRn extracellular domain at pH 6, determined by a label-free surface plasmon resonance-based assay (Biacore™).

Anti-TNF	Affinity (K_D), mean ± SD[a]
Infliximab (IFX)	132 ± 23 nM
Adalimumab (ADA)	225 ± 33 nM
Etanercept (ETA)	1500 ± 323 nM
Certolizumab pegol (CZP)	No binding
Non-PEGylated CZP Fab'	No binding

Dissociation constant (K_D) was calculated from the monovalent binding kinetics measured at 6 concentrations.
[a] 12 replicate experiments.

within the range of values reported from similar assays (Gurbaxani et al., 2013). In comparison, the binding affinity of ETA to FcRn was approximately 5–10-fold lower than that observed for the monoclonal antibodies (Table 1; Fig. 2C). This is similar to the dissociation constant previously reported (Suzuki et al., 2010). In contrast to the other anti-TNFs tested, CZP (PEGylated and non-PEGylated) did not bind to the FcRn with any measurable affinity (Table 1; Fig. 2D and E).

3.2. In vitro *human FcRn-mediated transcytosis of anti-TNFs*

FcRn-mediated transcytosis of the monoclonal antibodies was found to be greater than that for the other types of anti-TNFs tested (Fig. 3). ETA transcytosis was less than that of both ADA and IFX, and the level of CZP transcytosis was significantly lower than that observed for all the other anti-TNFs tested (Fig. 3). The negative control antibody (P146) also demonstrated a low level of transfer (Fig. 3), similar to that observed for CZP.

3.3. Ex vivo *placental transfer of CZP*

Placental perfusion was validated for transport capability by demonstrating steady-state, materno-fetal transfer of the positive control anti-D IgG. The anticipated perfusion success rate is approximately 40%, and 11 out of 18 placentas achieved closed-circuit perfusion for ≥4 h. Of these perfusions, 6 showed significant anti-D IgG transport (Table 2), and the transfer fraction average was 0.41 ± 0.24% (n = 6; mean ± SD); data are shown for the sample taken at the last time point assessed when anti-D IgG transfer was highest. Both the rate and total amount of anti-D IgG transport were typical (Duncan et al., 1995), despite the presence of CZP, indicating no apparent inhibitory effect of CZP on the placental transfer of IgG.

Mean duration of closed circuit perfusion was 5 h, and the longest perfusion duration in a single placenta was 13 h (Placenta 2, Table 2). There were no unusual findings upon visual inspection

Table 2
Ex vivo placental transfer of anti-D IgG and certolizumab pegol (CZP) from maternal to fetal circulation (data shown are from the sample taken at the last time point assessed when anti-D IgG transfer was highest, which was the final perfused hour in all cases).

Placenta number	Perfusion time (hours)	Anti-D IgG transport (%)	CZP transport (%)
1	6	0.002	<0.21[a]
2	13	0.26	<0.21[a]
3	4	0.06	<0.21[a]
4[b]	4	0.53	0.46
5	5	0.46	<0.21[a]
6	5	0.74	<0.21[a]

[a] Below lower limit of quantification.
[b] This placenta showed evidence of breakdown of the fetal capillary bed and non-specific leakage (leakage to another area of the placenta other than the lobule being perfused) from the fetal to the maternal circuit.

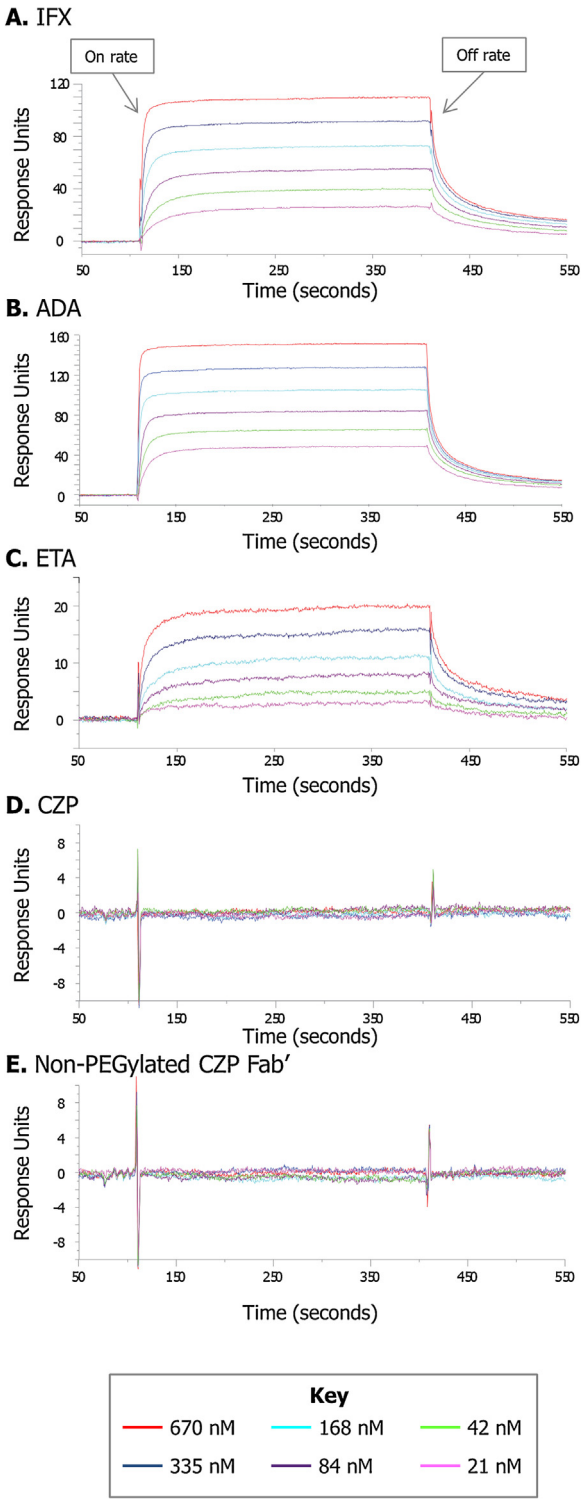

Fig. 2. Representative kinetics of human FcRn binding by anti-TNFs.
High binding affinities for FcRn were found with the monoclonal antibodies IFX and ADA; the binding affinity of ETA to FcRn was approximately 5–10-fold lower than that observed for the monoclonal antibodies, whereas CZP (PEGylated and non-PEGylated) did not bind to the FcRn with any measurable affinity. Abbreviations: CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; ETA, etanercept.

of the placental architecture in Placenta 2 compared with the other placentae. The concentration of CZP in maternal circuits remained between 40 μg/mL and 200 μg/mL (the starting concentration) during perfusion, somewhat higher than normal CZP plasma concentrations in patients treated in the clinic (FDA, 2014). The pH of

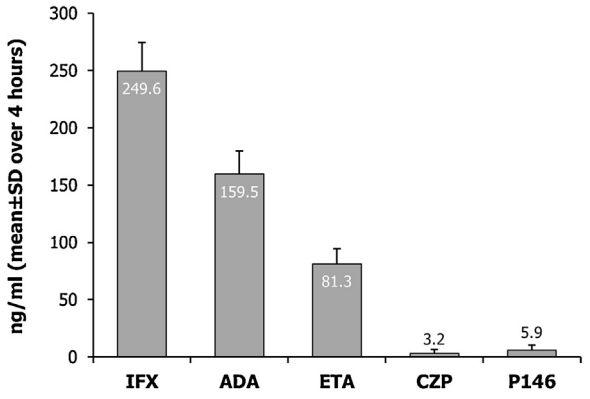

Fig. 3. *In vitro* transcytosis of anti-TNFs across a MDCK II cell monolayer engineered to express human FcRn and B_2M (ng/mL over period of 4 h; mean ± SD, n = 3). ETA transcytosis was less than that of both ADA and IFX, and the level of CZP transcytosis was significantly lower than that observed for all the other anti-TNFs tested. The negative control antibody (P146) also demonstrated a low level of transfer, similar to that observed for CZP.
Abbreviations: P146, negative control antibody; CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; ETA, etanercept.

both fetal and maternal arterial supply and venous returns were measured at the end of perfusion and, in the 6 placentas, ranged from: pH 6.8–7.1 in the fetal arterial supply; pH 6.7–7.5 in the fetal venous return; pH 7.3–7.8 in the maternal arterial supply, and pH 7.2–7.6 in the maternal venous return. Fetal loss ranged from 0.22–0.73 mL/min. In 5 of the 6 placentas that demonstrated anti-D IgG transfer, the level of CZP in the fetal perfusate was below the lower limit of quantification by ELISA for the entire duration of perfusion (Table 2). The remaining placenta demonstrated measurable CZP materno-fetal transfer (Table 2), however, visual inspection of placenta number 4 suggested breakdown of the fetal capillary bed, which was supported by observed excessive loss from the fetal reservoir.

4. Discussion

Given the key role played by FcRn binding of IgG Fc-region in the active placental transport of antibodies (Roberts et al., 1990; Simister and Story, 1997; Saji et al., 1999), we compared FcRn binding for a variety of anti-TNFs. The anti-TNFs tested fell into three broad structural categories: monoclonal antibodies (ADA and IFX), a TNF receptor-IgG Fc fusion protein (ETA) and a monoclonal antibody Fab' fragment (CZP). The monoclonal antibodies IFX and ADA were found to have high affinity for FcRn, which is unsurprising, given their intact Fc-region. The TNF receptor-IgG Fc fusion protein ETA, which also has an Fc-region, exhibited a lower affinity for FcRn compared to the monoclonal antibodies, although binding was still measurable. This reduced affinity for FcRn has been reported previously, and may be due to fusion of the TNF receptor to the Fc-region either altering the conformation of the binding region or causing steric hindrance, which in turn interferes with FcRn binding (Suzuki et al., 2010). In contrast, CZP, which lacks an Fc-region, did not bind FcRn with any measurable affinity. As CZP is also PEGylated, in order to prolong plasma half-life (Bourne et al., 2008), we confirmed that the PEGylation cannot be responsible for the lack of FcRn binding, given the non-PEGylated CZP Fab' also demonstrated no measureable FcRn binding.

The hypothesis that the inability of CZP to bind FcRn consequently leads to a lack of active drug transport was tested *in vitro*, where a direct relationship was observed between FcRn binding affinity and the amount of anti-TNF actively transported. IFX and ADA, which possess high binding affinity for FcRn, and ETA, which has lower, but measurable affinity for FcRn, all demonstrated FcRn-mediated transcytosis. In contrast, transcytosis of CZP was substantially lower and comparable to transport of a negative control antibody (P146), which was modified to prevent FcRn binding.

Given that neither the negative control antibody nor CZP bind FcRn, the levels of CZP detected in this assay are possibly due to a low level of non-specific leakage across the cell layer, rather than active receptor-mediated transport. These results also support the hypothesis that the low levels of CZP placental transfer reported in patients (Mahadevan et al., 2013) may be due to the lack of binding to FcRn preventing active transport. This is in contrast to IFX and ADA, which demonstrated relatively high binding affinity to FcRn, and were previously reported to undergo materno-fetal transfer (Mahadevan et al., 2013).

We also directly tested materno-fetal transfer of CZP in an *ex vivo* human placental transfer system, and results indicate very low levels of CZP transfer from maternal to fetal circulation. Since this was expected, the concentration of CZP added to the maternal circulation was much higher than would be observed in clinical use to facilitate detection. As a result, CZP concentrations in the maternal circulation were between 40 and 200 μg/mL (the starting concentration) during perfusion, whereas mean peak plasma concentrations reported in RA patients receiving CZP according to prescribing information (*i.e.* loading dose of 400 mg subcutaneously at weeks 0, 2 and 4, followed by 200 mg every other week) are between 43 μg/mL and 49 μg/mL (FDA, 2014). In the placentas where CZP transfer was detected, excessive loss of the fetal reservoir and evidence of breakdown of the fetal capillary bed were noted, suggesting non-specific leakage into the maternal circuit. However, the level of materno-fetal CZP transfer still remained below that seen with the anti-D IgG control. We hypothesize that the inability of CZP to bind FcRn could account for the observed differences between the placental transfer of the anti-D IgG control and CZP.

This hypothesis also offers an explanation for reported low levels of *in utero* CZP placental transfer, compared to other anti-TNFs (Mahadevan et al., 2013). In this clinical study, low CZP serum concentrations (< 2 μg/mL) were found in both infant and cord blood (median ratio of cord-to-maternal CZP level was 3.9% [range 1.5–24%]) at birth after CZP treatment during pregnancy to control inflammatory bowel disease. In comparison, concentrations of both IFX and ADA were significantly higher in both cord blood (160% and 153% of maternal plasma concentration for IFX and ADA, respectively) and infants at birth. These results reflect similarities to the *in vitro* transcytosis and *ex vivo* placental transfer data described here and correlate with FcRn binding affinity. Together, these results suggest that a lack of FcRn binding prevents active transport of CZP, which leads to minimal placental transfer.

Given its reported minimal placental transfer, it has been recommended that CZP may be continued throughout pregnancy (Ng and Mahadevan, 2013). However, all use of anti-TNFs during pregnancy is currently not approved, and as clinical data are limited, uncertainty persists. The results from the present study support the conclusion that CZP does have a low propensity for materno-fetal transfer, perhaps the lowest placental transfer rate of current anti-TNFs; thereby providing an explanation for previous clinical observations (Mahadevan et al., 2013). Clearly, additional clinical data are required to fully assess the safety and tolerability of anti-TNFs in pregnancy. However, the findings of this study suggest the impact on the fetus is lessened by the unique structure of CZP and resultant extremely low placental transfer.

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