Background

Drug delivery to the brain is one of the greatest challenges in treating CNS disorders. A single-cell layer of endothelial cells forms a tightly regulated interface between the vascular system and central nervous system (CNS) known as the blood-brain barrier (BBB) (1). Penetration of monoclonal antibodies across this barrier into the brain interstitial space is low.

The transferrin pathway allows the transport of iron molecules across the BBB via the binding of iron-bound transferrin to transferrin receptor and transcytosis across the brain endothelial cell (BEC). Manipulation of this pathway by binding to its components has allowed the transport of large molecules such as antibodies across the BBB experimentally.

Bi-specific antibodies which utilize anti-TFR as brain targeting arm and anti-BACE1 (an enzyme cleaving amyloid precursor protein) as therapeutic arm have been reported in the literature.

Recently, Kanodia et al. published a cymolgous monkey model for anti-BACE1 antibodies where they showed that very potent antibodies to the transferrin receptor had lower pharmacodynamic effects in the brain compared to antibodies with weaker affinity due to TFR-mediated elimination in blood (3).

Methods

The 5-compartment brain model in Simcyp was modified by the addition of an endothelial cell compartment (Figure 1).

The following processes were modelled:

1) Binding of IgG to the transferrin receptor in the brain vascular compartment
2) Internalisation of the IgG-TFR complex in the endothelial cells
3) Release of IgG from the complex
4) Recycling or transcytosis of IgG by transferrin receptor
5) TMDD models were included in the systemic blood compartment and in the brain

Figure 1 depicts the modified 6-compartment brain model.

Amyloid-β turnover was modelled with an indirect response model and the effect of the antibody was modelled as inhibition of production of Amyloid-β. Peak effect is the maximum reduction of Amyloid-β. The average effect is calculated by the below equation

\[ \text{Average Inhibition} = 100 \times \frac{A_{\text{Baseline,AUC}} - A_{\text{AUC}}}{A_{\text{Baseline,AUC}}} \]

Aims

Our aim was to see if the full PBPK model with the 6-compartment creates the same trend as observed in the publication by Kanodia et al.

Results

Spinal CSF to plasma ratio data was extensively collected from the literature for IgG, Albumin and various other small and large proteins. The hydrodynamic radius was calculated with the default Simcyp equation. Figure 2 shows the observed vs. the predicted Spinal CSF to plasma data. The predicted Spinal CSF: Plasma ratio correctly predicted the observed values.

Discussion

• Using a full PBPK model and accounting for TFR transport the experimental relationship between TFR potency and PD effect was simulated.
• This type of modeling can be performed for other bi-specific antibodies
• Different relationships between maximal and average PD effect and TFR binding potency were observed.

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References


Figure 1. 6-Compartment brain model

Figure 2. Spinal CSF to Plasma Ratio in Humans

Figure 3. A. Plasma and brain ISF concentration when antibody-transferrin receptor k₈ of 3nM. B. amyloid-β inhibition at 3nM k₀. C. Plasma and brain ISF concentration at k₀ of 30,000nM. D. amyloid-β inhibition at 30,000nM k₀. E. Plasma and brain ISF concentration without TFR binding. F. amyloid-β inhibition without TFR binding.

Figure 4. Average (Blue) and Peak (Red) inhibition of amyloid-β at 30 mg/kg dose of anti-TFR antibody with the same BACE1 arm but with varying affinity to transferrin receptor.