PK/PD MODELLING OF BNABS FOR HIV TREATMENTS IDENTIFYING KNOWLEDGE GAPS

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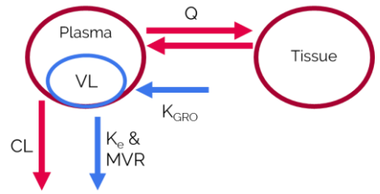
Introduction

- Broadly neutralizing antibodies (bnAbs) are anti-HIV monoclonal antibodies (mAbs) under investigation whereby concentrations at clinically effective doses often exceed their in vitro potency by more than 10-fold.
- Pharmacokinetic and pharmacodynamic (PK/PD) modelling is critical to drug development. Application of relevant antibody models to bnAbs, incorporating pre-existing HIV and mAb knowledge, may identify knowledge gaps and solutions.
- A review of infectious disease models led to the identification of a common model structure.[1] In all cases, models described a drug-induced decline of a pathogen; observed clinical trial data were similar to viral load (VL) declines seen with bnAb monotherapy in viremic patients. These models also included emerging pathogen resistance, alterations in PK etc,[2,3] aspects similar to HIV models. One key aspect was identification of a threshold (MIC in antibacterials, MPC in malaria etc) which correspondingly can be used to evaluate bnAb dose and duration.
- Aim: Characterize the efficacy of bnAbs and to anticipate the effects of various physiological processes by applying a common model structure of infectious disease.

Methods

A review of infectious disease models identified a unified PK/PD scaffold, adapted to fit published in vivo bnAb (BNC117) PK and PD data (Fig 1.). A non-linear mixed effects approach was used with the model to predict bnAb data obtained from patients with detectable viral load.[4] The model was then used to predict, using the same parameters, the time of appearance of virus in suppressed patients[5] who were switched to 3BNC117. Predictions were made by simulating 5000 participants with their own PK and efficacy parameters drawn from the modelled distributions. Sensitivity analyses evaluated the impact of tissue biodistribution, accelerated antibody clearance and resistance on parameter and dose estimation.

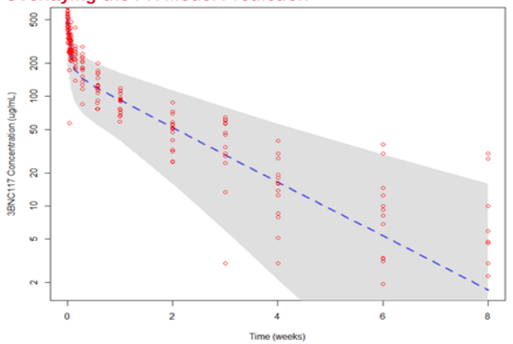
Figure 1. The PK/PD Model Structure Used in the Analysis of 3BNC117 PK Data and Its Effects on VL Measured in the Plasma



Red Figures = PK, Blue Figures = VL, Plasma & Tissue & VL= Compartments, Q = Intercompartmental Clearance, CL = Clearance, K_{gro} = Growth Rate of VL, K_e and MVR = Intrinsic VL decline (K_e) and Maximal Viral decline Rate (MVR)

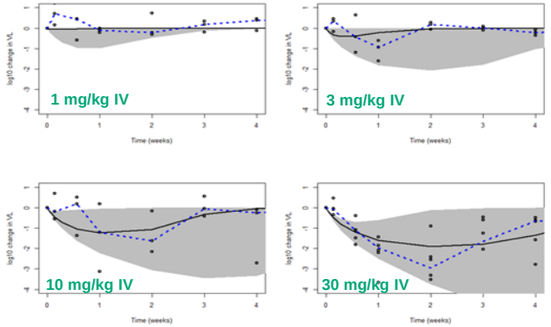
References: 1. Nielsen, E.I. and Friberg, L.E., 2013. Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. *Pharmacological reviews*, *65*(3), pp.1053-1090. **2.** Baker M. (2012) Lost in translation? Bridging the preclinical / clinical divide. *Malaria Journal* 11 (Suppl 1). **3.** Rathi, C., et al., 2016. Translational PK/PD of anti-infective therapeutics. *Drug Discovery Today: Technologies*, *21*, pp.41-49. **4.** Caskey, M., et al., 2015. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. *Nature*. *522*(7557), p.487. **5.** Scheid, J.F., et al., 2016. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. *Nature*, *535*(7613), p.556.

Figure 2. Observed Dose-Normalised 3BNC117 Plasma Levels Following IV Dosing (1, 3, 10 and 30 mg/kg) Overlaying the PK Model Prediction



Blue line = geometric mean, grey shading = 5th – 95th prediction interval.

Figure 3. Observed Log-Change in VL in Viremic Patients Following IV Dosing of 3BNC117 (1, 3, 10 and 30 mg/kg) Overlaying the PK/PD Model Prediction



Black and blue lines = predicted and observed geometric mean, grey shading = 5th – 95th prediction interval, points = observed data.

Figure 4. Box and Whisker Plots of (A) the Model Predicted Observed and Predicted 3BNC117 IC90 and Distribution Overlaid With Individual Data, and (B) the Week Two Predicted and Observed 3BNC117 Concentrations

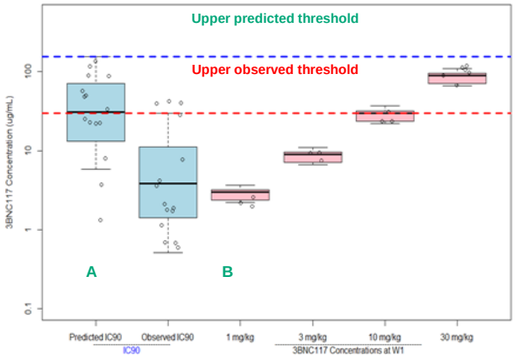
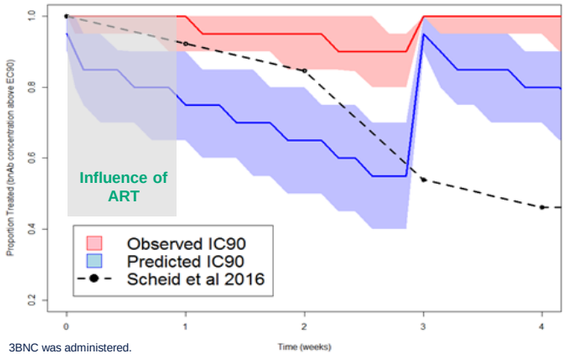


Figure 5. Model-Based Predictions of VL Appearance in Suppressed Patients After Their Change From ART to 30 mg/kg 3BNC117



3BNC was administered.

Discussion and Conclusions

The bnAb model had a structure common to infectious diseases and was capable of predicting viral decline and viral rebound. The model identified viral dynamics, bnAb resistance, and lymphatic disposition as vital processes. In vivo bnAb potency was greater than in vitro estimates and warrants further evaluation. The individual potency estimates were critical vs use of an average potency – especially considering the range of the potencies by participant and between participants. Improvements in bnAb potency would be beneficial conferring lower doses and resilience to resistance.

Results

- Figure 1 illustrates the simplest common model identified, capable of characterising PK and pathogen dynamics, but excluded viral resistance, PK factors etc, reflecting the data available.
- The PK model predicted 3BNC117 PK parameter estimates similar to what was observed with other mAbs (Figure 2, CL = 13.7 days).
- The dose dependent effects of 3BNC117 on viral load were predicted with an increasing VL decline as 3BNC117 doses increased (Figure 3). An 'effective' IC_{50} was estimated - indicative and linked to the time and concentration dependency of nadir of the viral load decline.
- Estimated median 'effective' IC_{50} in blood was 17.3 µg/mL vs. median of 2 µg/mL from published clinical isolate data.[4] The equivalent IC_{90} (90th prediction limit) was 28 (154) and 3.9 (30) µg/mL, respectively, for model predicted and observed IC_{90}s (Figure 4).
- The log-linear decline in VL was maximal when 3BNC117 concentrations were above the IC_{90}-IC_{95}.
- Figure 4 illustrated that the variance in potency is significantly greater than PK resulting in variable VL decline (Figure 3). 3BNC117 concentrations at week 2 overlapped or fell below the predicted IC_{90} range with nadirs being observed before or by week 2.
- The model predicted that suppressed participants would experience viral rebound (Figure 5) once 3BNC117 concentrations fell below their IC_{50}. Influence of prior ART delayed the effect of transitioning to the bnAb, but observed data fell matching the predicted IC_{50} trace by week 3.

Table 1. A Sensitivity Analysis of Factors Affecting the PK/PD But Unable to Be Included in The Model

Factor	Affect on PK	Affect on Potency	Consequence	Remedy
Immunogenicity	↓↓	⇔	PK will unpredictably and rapidly decline shortening T>threshold making a monotherapy	Rapid treatment adjustments will be required
Lymphatic source of virus	⇔	↓IC_{50} The apparent efficacy (effective in the lymphatics) will increase representing a smaller effect compartment	PK models will have to infer lymphatic drug concentrations	Lymphatic and tissue drug levels will need to be determined
Resistance	⇔	↑IC_{50}	IC_{50} will increase making threshold higher and drug levels less effective	Increase dose across population to allow for possible resistance and increase in IC_{50}

- A sensitivity analysis, incorporating theoretical resistance, PK changes and a requirement for lymphatic treatment (Table 1) indicated that all three processes are critical for characterization.
- A decline in PK diminishes bnAb effectiveness – critical for immunogenicity. Resistance increased the IC_{90}, requiring higher doses and/or a difference between trough and threshold to allow for resistance. A lymphatic effect compartment (where bnAb has majority effect) would also fit the data and possibly have an IC_{90} closer to observed data.