

Benefits of TDM in clinical management: a test case in infliximab for ulcerative colitis (II-74)

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BACKGROUND

- Infliximab (IFX) is an anti-TNF α antibody used in the treatment of ulcerative colitis. A correlation between IFX exposure and clinical response in induction phase exists, and was further quantified through a PK/PD model (presented at PAGE 2018, III-74).
- The measure for clinical response used in the modeling is the Mayo endoscopic sub-score, with values of 0 (inactive), 1 (mild), 2 (moderate) or 3 (severe). Mucosal healing (MH) is defined as a score of 0 or 1.

OBJECTIVES

- To quantify the potential improvement in probability of mucosal healing (pMH) for different treatment regimen.
- Hypothesis: TDM will improve drug efficacy. This can be easily shown in an exposure-controlled clinical trial.

METHODS

- PK Model** The model is a 1cpt model (Ke=0.0549/day; V=6.87L) with between-subject variability (BSV) (CVs%=29 on Ke, 29 on V) and within-subject variability (WSV) (CVs%=19 on Ke, 0 on V). The full model with covariate effects was used: Ke was impacted by baseline score, C-reactive protein (CRP) and albumin (SA); V was impacted by sex.
- PD Model** The model predicts disease score at time of endoscopy, through an ordered transition model. Transition probabilities are influenced by cumulative area under curve (CAUC) up to time of endoscopy.
- A goodness for simulation (GfS) evaluation was performed to identify potential caveats in simulated scenarios.
- Population simulations were performed to quantify the potential improvement of a candidate dosing scheme, using 500 replicates of 209 subjects each (N=104.500).
- Covariates were initialized from the database. Subject inter-individual variability was sampled from parameter distributions, and inter-occasion variability was resampled at each dose.
- To investigate the optimal dosing for Infliximab in this indication, different regimen were tested. In each regimen, the dose was administered at day 0, 14 and 42:

- 5mg/kg fixed dose
- 10mg/kg fixed dose
- Open loop dosing to target pMH=70%

A root finding function was used to find the required dose to give at day 0, 14 and 42 to achieve a predicted pMH of 70% at day 84, predicted by the model using the covariates of the subject.

- Closed loop dosing to target pMH=70%, using an evaluation at day 14

The open loop dose was used as the first dose.

At day 14, IFX concentration was sampled from model with residual error. The individual PK parameters were determined using MLE.

This was used to calculate the dose at the two following dosing occasions to achieve pMH of 70% at day 84. Future IOV was fixed to 0. No individual parameter uncertainty was used.

- Simulations were performed using Simulo v7.3 Expert. MLE and dose finding was performed using the tdmore framework, integrated within Simulo. Tdmore is available at github.com/rfaelens/tdmore

RESULTS

Goodness for Simulation

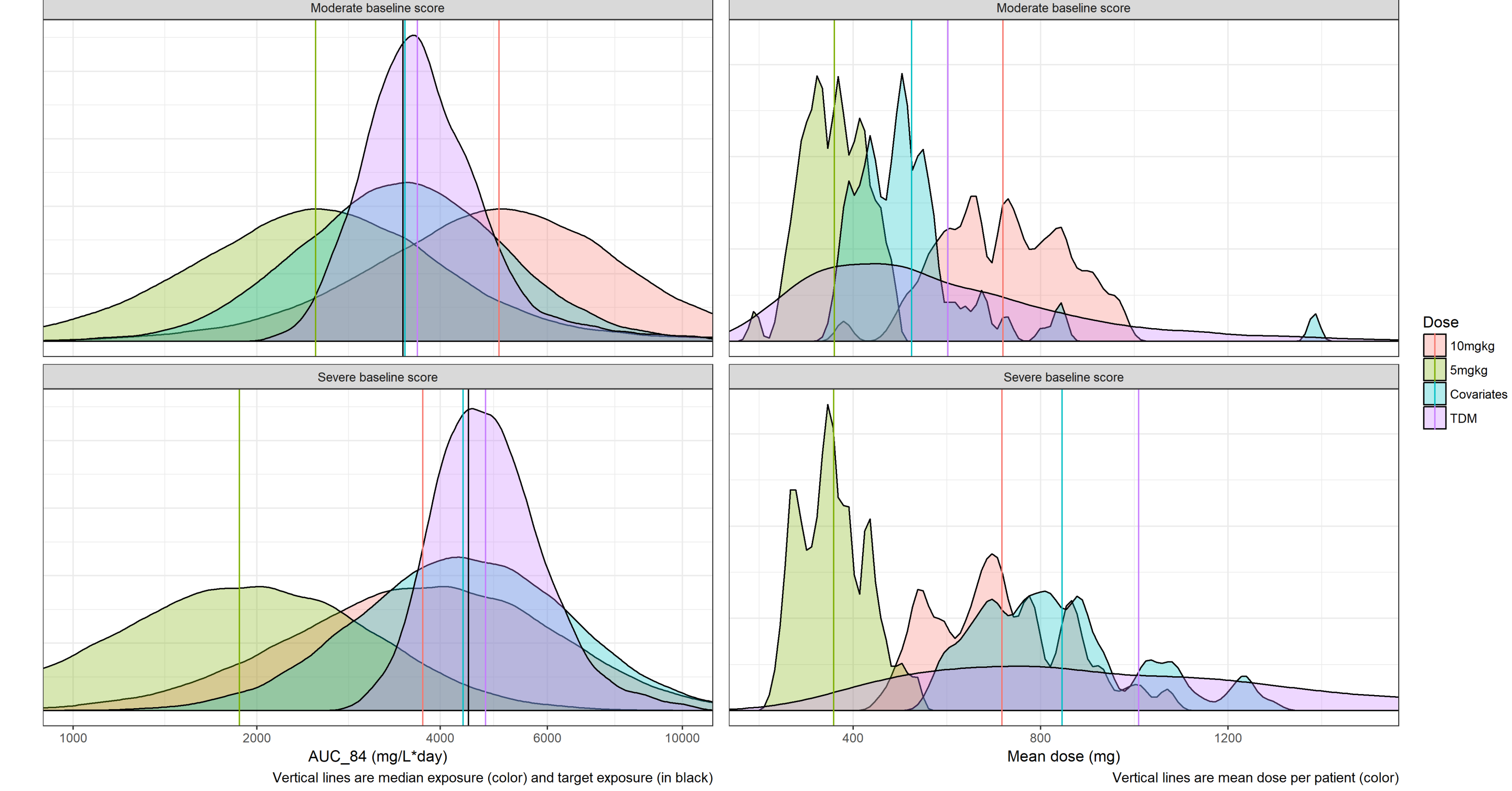
Source data The PD model was only trained on CAUC from [110, 6100]. 89% of doses were 5mg/kg. Results outside of this range should be interpreted with care.

Structural model Only a one-compartment model could be identified. Higher doses could result in target-mediated drug disposition, or a different occurrence of antibodies to infliximab.

Covariates Both CRP and SA are time-varying covariates associated with disease activity. Higher doses may result in higher pMH, lower CRP and higher SA, and therefore lower elimination rates and even higher exposures and pMH. By using the original covariates, we underestimated pMH.

Parameter uncertainty Parameter uncertainty is high for CRP and SA effects (24, 39 CVs% respectively). However, as these covariates have limited impact across the covariate range (CRP on Ke: -7.5% to 10.3%, albumin on Ke: 6.8% to -3.6%), a parameter sensitivity analysis was not deemed necessary.

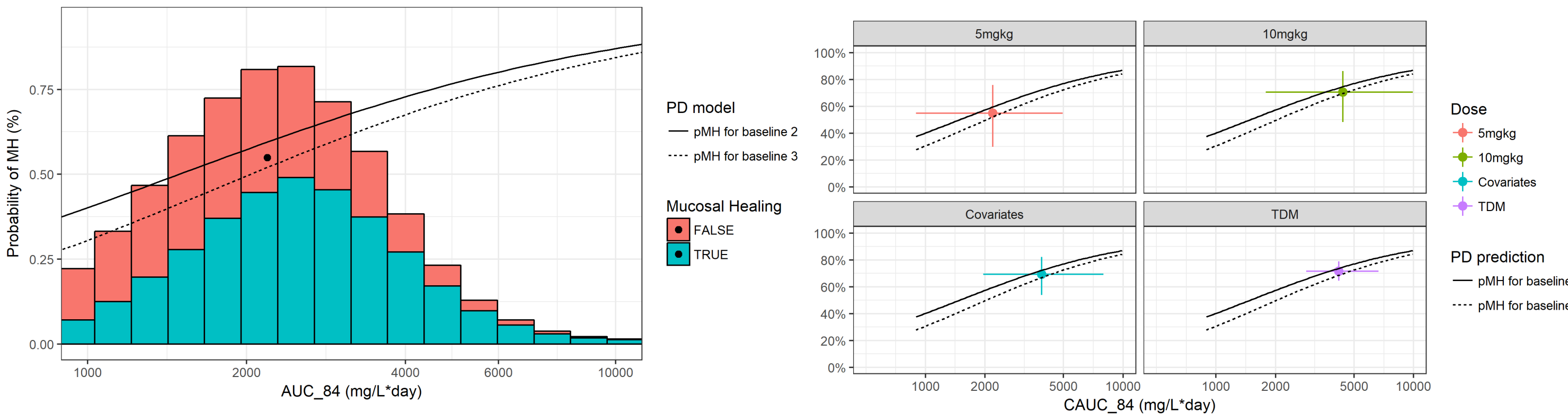
Predicted exposures for each treatment regimen



The 10mg/kg dose is too high for patients with moderate disease, yet too low for patients with severe disease. The covariate-adjusted dose hits the target, requiring 680mg on average per patient per dose.

TDM further reduces variability in exposure, at an increased drug usage (800mg).

Predicted probability of Mucosal Healing in the population



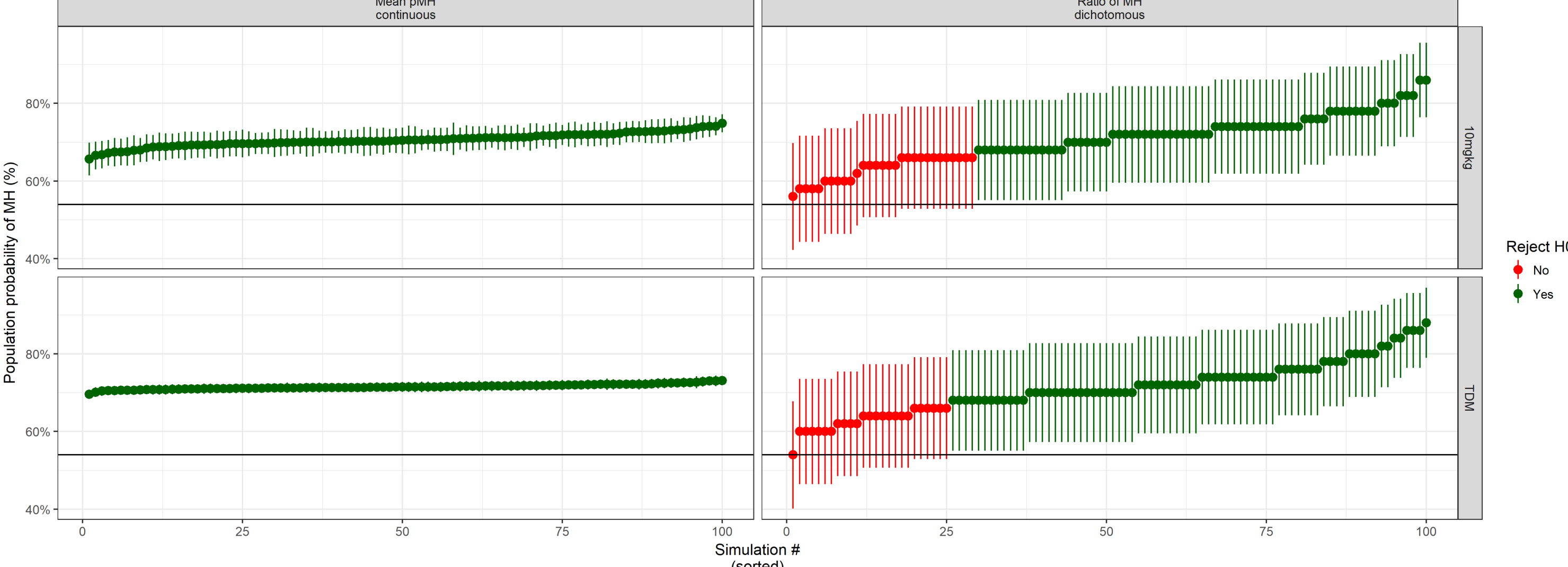
Left: Using the PD model, we can predict mucosal healing for each subject, based on his/her exposure.

Right: Open loop and closed loop adjustment reduces variability in exposure and endpoint. Due to the symmetric distribution for exposure, no improvement in population-average rate of mucosal healing can be observed. Individual variability is greatly decreased through dose adaptation though.

Trial simulation results

A head-to-head trial comparing 5mg/kg to 10mg/kg with N=50 subjects per arm has a PoSS of 71.6% (for p>0.05). 75 subjects are required for a PoSS=80%.

An exposure-controlled trial does not improve study power, because the dichotomous sampling error is the main cause of variability.



CONCLUSIONS

- A dose of 5mg/kg is predicted to result in pMH of 54%. Increasing the dose to 10mg/kg improves pMH to 70%.
- The dose can be individualized based on covariates or measured IFX concentrations. This reduces variability in exposure, improves individual pMH, but has no impact on population outcomes.
- A head-to-head trial comparing 5mg/kg to 10mg/kg requires N=YYY patients per arm (PoSS=80%). An exposure-controlled trial through TDM does not improve PoSS, due to the large uncertainty sampling a dichotomous endpoint.
- The proposed methodology allows quantification of the potential benefit of dose individualization. The resulting simulations can be used to design a trial to prove the benefit in a patient population.