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POPULATION PHARMACOKINETIC (PK) MODEL OF MYCOPHENOLIC ACID (MPA) AND ITS METABOLITE—MYCOPHENOLIC ACID GLUCORONIDE (MPAG) IN LONG TERM TRANSPLANT RENAL PATIENTS USING MONTE-CARLO PARAMETRIC EXPECTATION MAXIMIZATION (MC-PEM). O. O. Okusanya, PharmD, K. Dole, PharmD, J. Zack, PharmD, A. Forrest, PharmD, A. Gundroo, MD, N. Leca, MD, R. C. Venuto, MD, K. M. Tornatore, PharmD, University at Buffalo School of Pharmacy and Pharmaceutical Sciences, University at Buffalo School of Medicine and Biomedical Sciences, University at Buffalo School of, Buffalo, NY.

BACKGROUND: Notable inter- and intrapatient PK variability in MPA and metabolite, MPAG has implications on clinical outcomes in renal transplant recipients (RTR). Our objective was to evaluate population models and factors responsible for variability of MPA and MPAG PK in long-term RTR.

METHOD: 55 clinically stable RTR (18 African American (AA) and 22 Caucasian (C) males with 14 C females) receiving chronic MPA, cyclosporine, with or without prednisone at least 6 months post-transplant were sampled prior to, and 2, 4, 7, 9, and 12 hrs after an observed MPA dose. Samples were assayed using LC/MS assay for MPA and MPAG with a LLQ of 0.66 ng/mL and 11 ng/mL, respectively. Candidate PK models using a population analysis technique—Monte-Carlo Parametric Expectation Maximization implemented in S-ADAPT 1.53, were fit to the data. The data was weighed by the inverse of the estimated measurement error variance; model discrimination was by evaluating the difference in objective function (−2Log Likelihood) assuming a χ^2 distribution. Values less than the LLQ were modeled using the Beal M3 method. General Linear Modeling was used to evaluate covariates to be included in the model.

RESULT: A 2-compartment model with first order absorption for both the MPA and MPAG best describe the data. A recycling compartment did not result in a significant change in objective function. The goodness of fit was good, with overall r^2 of 0.812 and 0.968 for the MPA and MPAG, respectively. The following population parameters were estimated:

PARAMETER[2]	Mean[1]	% SE	CV %	% SE	PARAMETER[2,3]	Mean[1]	% SE	CV %	% SE
CLf (L/hr)	12.6	11.1	31.9	43.3	CLmFm (L/hr)	0.666	11.0	52.6	57.5
VcF (L)	10.7	90.8	60.2	292	VmFm (L)	5.92	30.4	42.2	44.0
VpF (L)	262	94.6	62.8	116	VpmFm (L)	0.274	134	72.0	227
CLdF (L/hr)	17.0	60.8	39.3	69.4	CLdmFm (L/hr)	9.35	51.9	96.4	90.9

[1]Geometric Mean.
[2]Estimates of MPA and MPAG are conditioned on Bioavailability (F).
[3]Estimates of MPAG are also conditioned on the amount of MPA absorbed converted to MPAG (Fm).

Race was a significant covariate with the clearance of MPA ($p < 0.001$) and MPAG ($p < 0.028$). CrCL and steroid use ($p < 0.05$) was also correlated with the clearance of MPAG and CrCL was strongly correlated with MPA volume ($p < 0.05$).

CONCLUSION: A racial influence was noted on MPA and MPAG PK, which can be best, modeled using a 2-compartment model with a first order rate constant of absorption. Further studies are ongoing to relate these parameters with immune response.

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POPULATION PHARMACOKINETICS OF CERTOLIZUMAB PEGOL. E. Pigeolet, PhD, P. Jacqmin, PhD, M. Sargentini-Maier, PharmD PhD, G. Parker, PhD, A. Stockis, PhD, UCB, Exprimo NV, UCB, Braine l'Alleud, Belgium.

BACKGROUND/AIMS: Certolizumab pegol (CZP) is a pegylated Fab´ fragment of a humanized anti-TNF antibody. The aim of the analysis was to identify demographic and physiologic determinants of the disposition of CZP, in Crohn's Disease (CD) patients.

METHODS: We evaluated 10275 plasma concentration-time records from 1580 subjects of whom 80% were patients with Crohn's disease, 15% rheumatoid arthritis and 5% healthy subjects. The structural model was a two compartment model with mixed order (between 0 and 1) absorption and first order elimination rates, and inter-occasion variability on clearance. Modeling was performed using NONMEM V with FO estimation.

RESULTS: Typical clearance was 0.428 L/day and distribution volume 4.0 L in a 70 kg subject. Age, gender, creatinine clearance, white blood cells count and concomitant drug treatment such as steroids, amino-salicylic acid and analogs or anti-infectives did not influence the pharmacokinetics of CZP. Anti-CZP antibodies, repeated administration, weight, monocyte count, immunosuppressant intake and ethnicity had a statistically significant effect on the pharmacokinetic model. Simulations from the final model showed that, at steady state, only the presence of anti-CZP antibodies had a more than 30% effect on C_{max} and AUCτ. However, these were detected in only 8% of the patients and did not appear to influence the efficacy endpoint (CDAI score). Doubling body weight, the second most influential covariate, was associated with a 25% and a 20% decrease in C_{max} and AUCτ, respectively.

CONCLUSION: In conclusion, amongst the numerous covariates tested for their contribution to the pharmacokinetic variability of CZP, none of them seemed to have a clinically relevant impact.

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QUANTITATIVE ASSESSMENT OF EXPOSURE-RESPONSE RELATIONSHIPS FOR THE EFFICACY AND TOLERABILITY OF VARENICLINE FOR SMOKING CESSATION. P. Ravva, H. Faessel, M. R. Gastonguay, T. G. Tensfeldt, K. Reeves, Pfizer Clinical R&D, Metrum Research Group LLC, Groton, CT.

BACKGROUND: The analysis goals were to characterize varenicline exposure-response (E-R) relationships for efficacy [continuous quit rates (CQR) for Weeks 4–7 (W47) and 9–12 (W912)] and tolerability [nausea overall incidence (NI) and weekly incidence (WNI)] in smokers. Findings were to be used to support dosing recommendations.

METHODS: Data from 5 randomized, placebo-controlled clinical trials in adult smokers were appropriately pooled for the population E-R analyses. About 600, 1900 and 2200 subjects representing both genders equally for the W47, W912 and NI/WNI endpoints, respectively contributed to these analyses. Because each of the pharmacodynamic endpoints (CQR, NI) was a dichotomous categorical variable representing the occurrence of an adverse event or a successful quit (1 = yes, 0 = no), logistic regression models were used to estimate the probability of response as a function of varenicline exposure (dose range 0.3-2 mg/day). Individual exposures [$AUC_{(0\text{-}24)_{ss}}$] were obtained from the final population pharmacokinetic model. A full model with covariates (baseline smoking status (FSQ1), race, sex and age) on the baseline probability was constructed. The covariate effect and precision of the model parameters were assessed using 95% bootstrapped confidence intervals (CI).

RESULTS: Higher varenicline exposure was associated with higher probability of W47 and W912 CQR after treatment. With increasing doses the probability of quitting for a reference population (White, Male, 45 yrs old and $FSQ1_{(6\text{-}30min)}$) increased from 22% (19–26%) in subjects receiving placebo to 38% [34–42%] at 0.5 mg BID and to 56% [51–61%] at 1 mg BID. This analysis also found that nausea incidence (mild to moderate severity) is positively associated with drug exposure and female gender. At 1 mg BID the estimated probabilities were 24% in males and 40% in females compared to their placebo rates of 7% and 14%, respectively. WNI was highest at Week 1 with a rate of 12.9%, which decreased progressively over time to a rate of 5% at Week 13.

CONCLUSIONS: An increased probability of quit was associated with greater steady-state exposure to varenicline. This E-R supported the recommended dose of 1 mg BID. The incidence of nausea was dose-dependent, and a trend towards decreasing probability of nausea incidence with time was evident.