Impact of genetic and non-genetic factors on the pharmacokinetics of intravenous immunoglobulin in patients with predominantly antibody deficiencies in Malaysia

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BACKGROUND

- The interpatient pharmacokinetic (PK) parameters of intravenous immunoglobulin (IVIG) varies widely causing difficulty in optimizing individual dosage regimen[1].
- This study aims to estimate the population PK parameters of IVIG and to investigate the impact of genetic polymorphism and clinical variability on the PK of IVIG in patients with predominantly antibody deficiencies.

METHOD

Data collection

- Blood samples = IgG levels for pharmacokinetic studies, genetic studies.
- Clinical data = patients' medical records.

Model development[2]

- Population PK modeling using Monolix® version 2019R1 with SAEM algorithm was used to estimate population pharmacokinetic parameters.
- Structural model: One- and two-compartment model
- Covariate investigated: Gender, ethnicity, weight, age, genetic polymorphism of the FcRn gene and presence of bronchiectasis[3].
- Covariate model: Combined stepwise forward selection and backward elimination approach.
- Model evaluation: Difference in OFV, GOF plots, VPC and bootstrap analysis.
- Monte Carlo simulation: To evaluate the probability of achieving target IgG trough of 5 to 10g/L using different dosing regimens of IVIG[1].

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RESULTS

- 30 IgG concentrations from 10 patients were analyzed.

Table 1: Characteristics of the patients (n = 10)

Characteristics		Median (min, max) or n (%)
Male		9 (90%)
Age, years		9.5 (3, 64)
Ethnicity	Malay Chinese Indian	6 2 2
Weight, kg		26.7 (9.3, 75)
IVIG dose, g		0.49 g kg^{-1} per dose, 3 – 4 weekly (0.36, 0.60)
FcRn	VNTR 3/3 VNTR 2/3	6 (60%) 4 (40%)
Bronchiectasis	Yes No	3 (30%) 7 (70%)

- The data were adequately described by a one-compartment model with linear elimination.

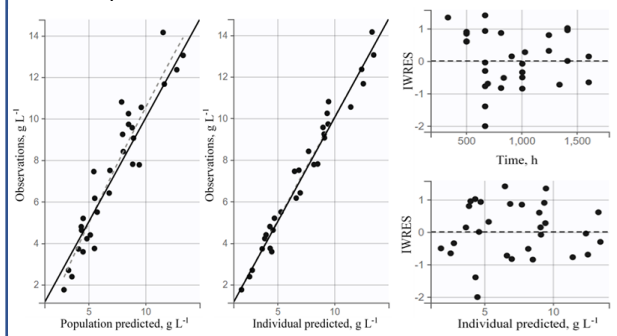

Figure 1: Goodness-of-fit plot for the final model

Table 2: Estimated population PK parameters

Parameter	Base model		Final model		Bootstrap estimate (90% CI)
	Value	RSE (%)	Value	RSE (%)	
Fixed effects					
Vd (L)	3.18	17.8	2.77	8.38	2.67 (2.38-3.05)
β_{Weight} (log L)	-	-	0.66	18.7	0.67 (0.043-0.92)
CL (L hr^{-1})	0.0025	20.8	0.0026	4.8	0.0026 (0.002-0.003)
β_{Weight} (log L hr^{-1})	-	-	0.88	8.24	0.89 (0.79-1.0)
Between-subject variability					
ωVd (CV%)	32.84	41.1	8.00	70.5	6.58 (3.1-12.75)
ωCL (CV%)	71.69	35.2	13.97	26.7	12.19 (5.2-16.72)
Residual variability					
Proportional (CV%)	12.65	19.7	10.23	16.9	9.87 (7.61-12.45)

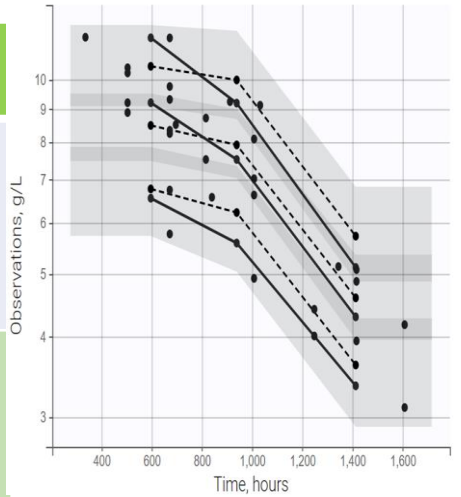

Figure 2: pcVPC with IgG concentration versus time based on 500 Monte Carlo simulations.

- Weight was an important covariate for Vd and CL.
- The final covariate model:-
  - Vd (L) = 2.77 x (Weight/27kg)$^{0.66}$
  - CL (L h^{-1}) = 0.0026 x (Weight/27kg)$^{0.88}$

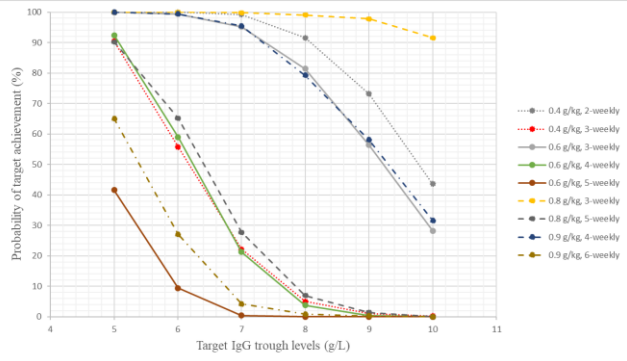

Figure 4: Target achievement analysis for IgG troughs of 5 to 10 g L^{-1} for various dosing regimens.

CONCLUSION

- A population PK model of IVIG in Malaysian PAD patients was established.
- Genetic polymorphism of the FcRn gene and the presence of bronchiectasis did not impact the PK of IVIG.
- The probability of achieving target concentration is higher when the dosing interval was reduced compared to increasing the cumulative dose.

REFERENCES

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