Validation of a Population pharmacokinetic model of recombinant factor VIII in boys with Haemophilia A

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INTRODUCTION

- Pharmocokinetic (PK) studies provide better estimation of drug activity than patient characteristics alone[1]
- PK of recombinant FVIII (rFVIII) traditionally use the:

ISTH 11-point protocol[2]: after a 72h washout administer 25-50 U/kg of rFVIII
11 samples taken at: 0, 15, 30, 60 mins AND 3, 6, 9, 24, 28, 32, 48 h
For Children do 5 point sampling instead at: 0, 1, 10, 24, 48 h
Non-compartmental model used.

- Population PK model has been proposed instead[1]
  - no washout required
  - fewer samples taken
  - Bayesian forecasting
  - Excellent correlation with ISTH method
- Point-of-care software now available to do population PK

METHODS

- Data from previously published cohort of 20 boys with Haemophilia A[3] was used as basis for study. That study evaluated PK of Kogenate-FS using the ISTH 11-point protocol after administering 50 IU/kg rFVIII
- From this a Population PK model was built by S. Bjorkman
  - $t_{1/2}$ and Cl: correlated with vWF:Ag ($p<0.01$) and not with patient age, weight, or mutation type
- For this study PK parameters ($t_{1/2}$, Cl) were re-calculated from study described above using:
  1. All 11 data points and non-compartmental model
  2. Population PK model with Bayesian analysis:
  - 11, 5 or 2 (24 & 28h or 28 & 32h) data points
- All these approaches to PK analysis were compared

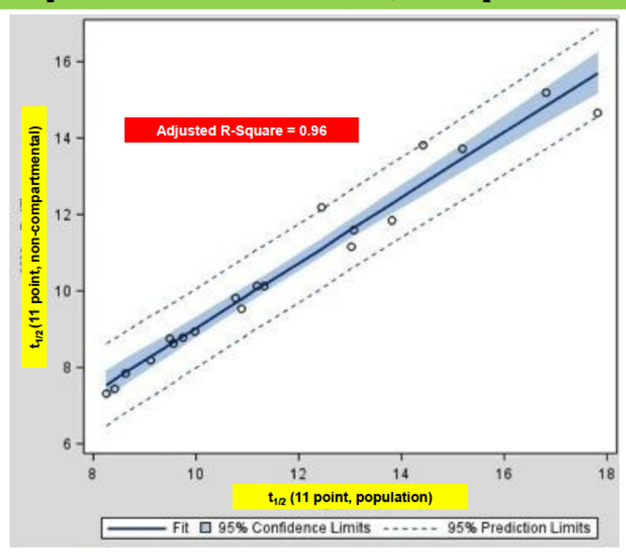
RESULTS

Variable	Interclass correlation coefficient	95% CI
Traditional vs Population PK Model (using all 11 sampling points)		
Clearance (Cl)	0.97	0.92 – 0.99
Half-life ($t_{1/2}$)	0.97	0.93 – 0.99
Comparing number of sampling points (using Population PK model)		
5 vs 11, Cl	0.999	0.997 – 0.999
5 vs 11, $t_{1/2}$	0.99	0.98 – 0.997
2 (24/28) vs 11, Cl	0.95	0.87 – 0.98
2 (24/28) vs 11, $t_{1/2}$	0.81	0.58 – 0.92
2 (28/32) vs 11, Cl	0.92	0.81 – 0.97
2 (28/32) vs 11, $t_{1/2}$	0.84	0.62 – 0.93

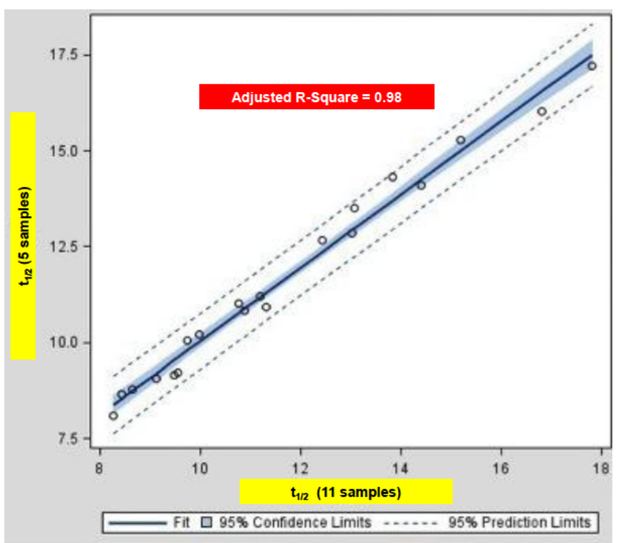
Interclass coefficient
0.7-0.8 = strong agreement
>0.8 = almost perfect agreement

Dataset from Barnes et al[3]:
median age 12.8y (4.4-18.1)
FVIII:C <1% n=15
FVIII:C 1-6% n=5

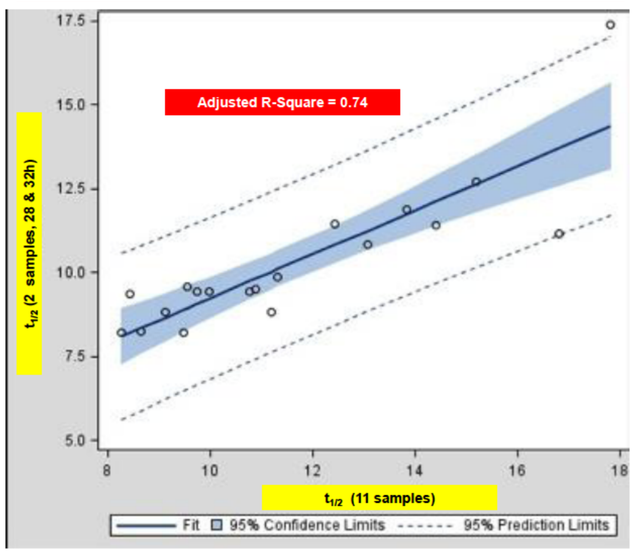
Non-compartmental vs population model, 11 points



11 vs 5 sampling points



11 vs 2 sampling points



CONCLUSIONS

- Bayesian analysis of Population PK model:
  - yields clinically similar data to traditional PK 11-point ISTH model
  - is more practical
    - no washout is required
    - fewer samples needed
  - requires prospective validation
    - of model
    - of point-of-care software, including dosing estimates

REFERENCES

1. BJÖRKMAN S. Haemophilia 2010; 119: 612–8; **2.** Lee M, et al. ISTH Website 21 March, 2001; **3.** Barnes C et al. Haemophilia; 2006; 12: 40–9.

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John Roy
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