

Exposure to the biological anti-thymocyte globulin (ATG) in children receiving allogeneic-hematopoietic cell transplantation (HCT): towards individualized dosing to improve survival



University Medical Center
Utrecht

R. Admiraal^{1,2,3}, C van Kesteren^{1,2}, MJD van Tol³, CM Jol van der Zijde³, RGM Bredius⁴, JJ Boelens¹, CAJ Knibbe²

Introduction

- Anti-thymocyte globulin (ATG) is used to prevent graft versus host disease (GvHD) and rejection in pediatric hematopoietic cell transplantation (HCT)
- Polyclonal, rabbit derived IgG antibody binds to antigens expressed by lymphocytes, monocytes and endothelium among others.
- Critical therapeutic window; overdosing leads to slow or absent immune reconstitution whereas underdosing may cause GvHD, both causing morbidity and mortality
- Blood concentrations are highly variable when dosing a fixed amount per kilogram over the entire population, with older children reaching higher concentrations

Aim:
Development of an evidence based dosing regimen to improve outcome in pediatric HCT through population PK/PD modeling

Data summary and Model

	Utrecht	Leiden	Total
Patients	130	77	207
Sex=M	74	46	120
Median age (years)	5.8	7.45	6.4
Range	0.1-22.7	0.6-17.7	0.1-22.7
Median weight (kg)	21	21	21
Range	3.66-96.0	6-72.0	3.66-96
Diagnosis			
Malignancies	53	43	96
Immunodeficiency	31	13	44
Bone marrow failure	14	4	18
IEM/benign hematology	30	17	47
Autoimmune	2	0	2
Median dose ATG (mg/kg)	10.5	10.1	10.3
Range	5-25.5	5-21.1	5-25.5

2-compartment model with linear elimination, where:

$Cl=Cl_{21\text{ kg}} * (BW/21)^{e1}$

$V1=V1_{21\text{ kg}} * (BW/21)^{e2}$

Table 1: Patient characteristics

Results

Table 2: Estimated parameters, relative standard error (RSE) and ETA shrinkage		Estimate	RSE (%)	Shrinkage (%)	Bootstrap*
	Cl (L/day)	3.7	6		3.7 (3.3-4.1)
	V1 (L)	7.9	11		7.9 (5.8-10.1)
	V2 (x V1) (L)	2.2	16		2.3 (0.8-3.6)
	Q (L/day)	22.7	25		24.5 (5.2-40.3)
	e1 in $Cl=Cl_{21} * (BW/21)^{e1}$	0.49	16		0.48 (0.33-0.65)
	e2 in $V1=V1_{21} * (BW/21)^{e2}$	0.63	11		0.62 (0.48-0.77)
	IIV CL (%)	76.6	6	4	76 (68-85)
	IIV V1 (%)	65.9	8	11	66 (54-76)
	IIV Q (%)	100.0	12	35	100 (51-132)
	Proportional residual error 1 (%)	28.1	6	11	28 (25-31)
	Proportional residual error 2 (%)	34.2	13	14	34 (23-42)

* n=1000, 95% successful, median (95% CI)

Correspondence:
C.A.J. Knibbe, PharmD, PhD
Department of Pharmacology
Leiden Academic Centre for Drug Research
Leiden, The Netherlands
c.knibbe@antoniusziekenhuis.nl

¹ Department of pediatric immunology, Universital Medical Centre Utrecht, The Netherlands
² Department of Pharmacology, Leiden Academic Center for Drug Research, Leiden, The Netherlands
³ Pediatric Immonology Labarotories, Leiden University Medical Center, Leiden, The Netherlands
⁴ Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

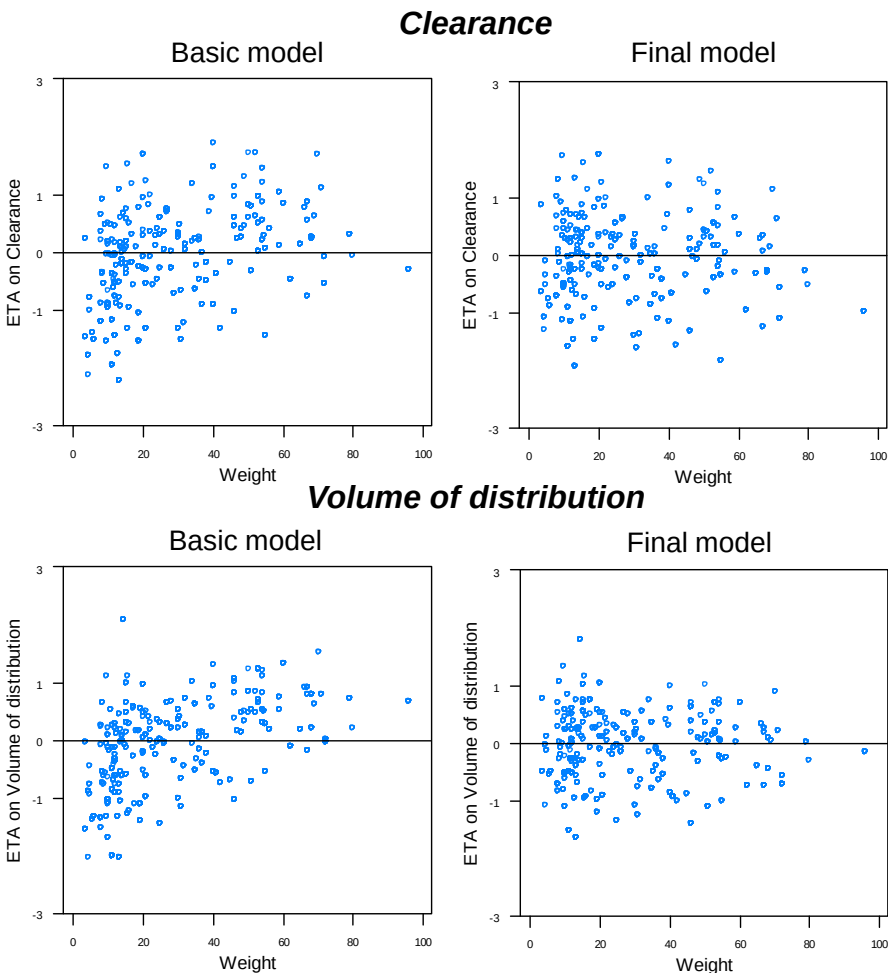


Fig. 1: ETA-distribution vs Weight before (basic model) and after (final model) inclusion of weight in an exponential function

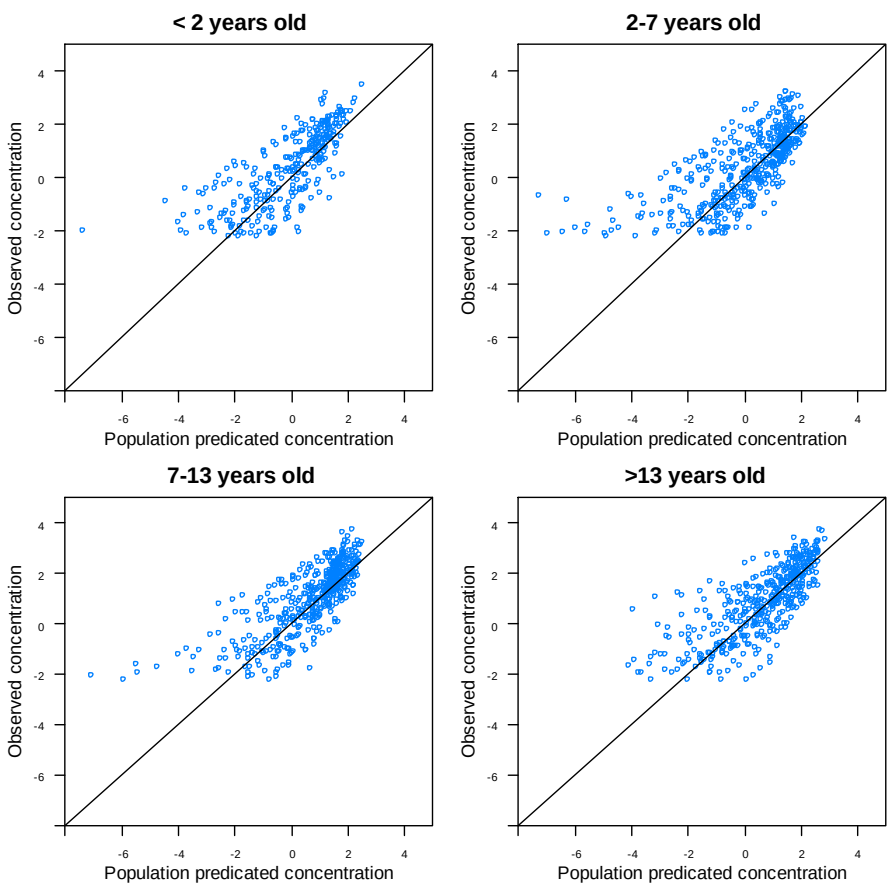


Fig 2: Population predictions versus concentrations in different age groups

Conclusions

- ATG pharmacokinetics can be well predicted using a 2-compartment model with linear clearance
- Weight is an important covariate on both clearance and volume of distribution



LEIDEN UNIVERSITY MEDICAL CENTER