Population pharmacokinetics of anti-thymocyte globulin (ATG) in children receiving allogeneic-hematopoietic cell transplantation: towards individualized dosing to improve survival

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Introduction: Challenges in pediatric HCT

- Reducing the toxicity of HCT:
  - Short term toxicity
  - Long term toxicity
- Improving efficacy
  - Better disease control

Balancing optimal disease control and reduced toxicity

Introduction: ATG (Thymoglobulin®)

- In vivo lymphodepletion
- Thymoglobulin® (anti-thymocyte globulin, ATG)
  - Different brands ATG; horse or rabbit derived
- Polyclonal rabbit derived IgG antibody
- Very broad range of targets
  - T-lymphocytes
  - Other lymphocytes
  - Epithelium etc.
- ~9% of ATG directed against human targets (active ATG)

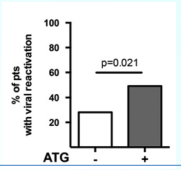
Introduction: ATG (Thymoglobulin®)

- Critical therapeutic window:
  - Underdosing
    - GvHD
    - Rejection
  - Overdosing
    - Delayed immune reconstitution, infection
    - More relapse (↓ Graft vs Leukemia)

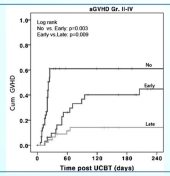
Introduction: outcome

Pediatric UCB transplants
- No ATG
- Early ATG (day -9 to -5)
- Late ATG (day -5 to 0)

Comparable EFS/OS *a*



a



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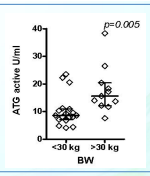
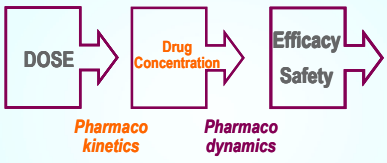


b

a. Lindemans et al Blood 2014 *b.* Jol et al BMT 2009

Introduction: PK/PD



Dose is often a poor descriptor of response

Project aim

- Describing the pharmacokinetics of active Thymoglobulin in pediatric HCT
- Explore the influence of weight and other factors on PK
- First step in development of individualized dosing regimen
- Evaluate current dosing regimen of Thymoglobulin®

Learning Objective

Describe the effect of weight on the pharmacokinetics of active Thymoglobulin®

Methods

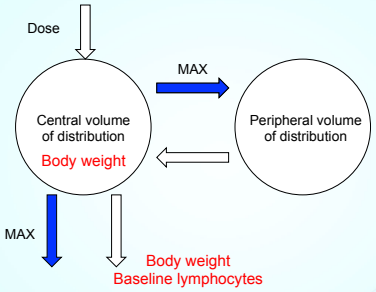
- Patients treated from 2004 to 2012 at two pediatric SCT-units in the Netherlands
- Serum active Thymoglobulin® concentrations quantified by flow cytometry
- Population pharmacokinetic (PK) modelling (NONMEM)
  - Population mean
  - Between patient variability
- Covariates influencing variability
- Model validation with advanced methods (bootstrap, NPDE)
- Simulations

Results: patient characteristics

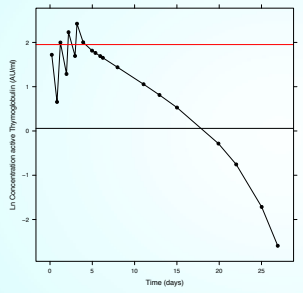
	Leiden	Utrecht	Total
Number of patients (n)	153	114	267
Number of HCTs (n)	159	121	280
Male sex (%)	67	57	62
Age (years)	6.5 (2.7-12)	5.9 (1.7-13.9)	6.5 (2.3-12.6)
Weight (kg)	21 (13-38)	20 (12-46)	21 (13-40)
Number of samples [n (mean per patient)]	2352 (15)	761 (6)	3113 (11)
Starting day ATG (days before transplantation)	5 (4-6)	5 (4-7)	5 (4-6)
Diagnosis (%)			
Malignancy	50	42	46
Immune deficiency	16	24	19
Bone marrow failure	4	10	6
Metabolic disease	0	21	9
Benign hematology	30	1	18
Auto-immune disease	0	2	1
Stem cell source (%)			
Bone marrow	63	29	48
Peripheral blood stem cells	23	5	15
Cordblood	14	60	34
Cordblood plus haplo or 2nd cordblood	0	6	2
Leucocyte count before conditioning (x 10^9)	3.7 (2.3-5.7)	4.5 (2.7-7.1)	4 (2.3-6.4)
Lymfocyte count before conditioning (x 10^9)	0.88 (0.29-2.14)	0.87 (0.26-2.71)	0.87 (0.28-2.5)

Shown as median (interquartile range) unless otherwise specified

Results: PK-model 1



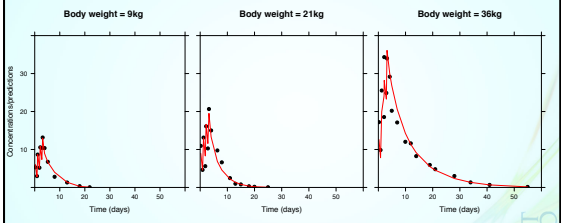
Results: PK-model 2



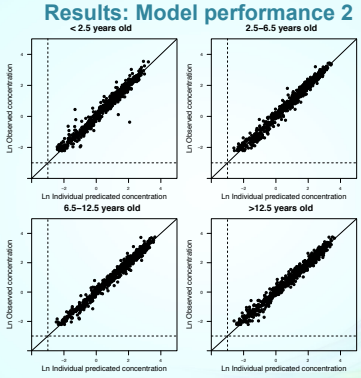
Tm
(Intercompartmental distribution)

Km (Clearance)

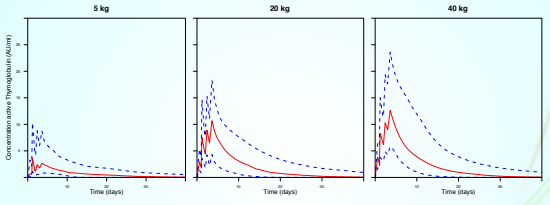
Results: Model performance 1



Results: Model performance 2



Simulations



- Current dosing regimen
  - Cumulative 10 mg/kg Thymoglobulin® over 4 days
- Higher exposure with higher weight!

Audience Response Question

A cumulative dose of 10mg/kg Thymoglobulin® over 4 days, the current dosing regimen, leads to a constant exposure in all age groups

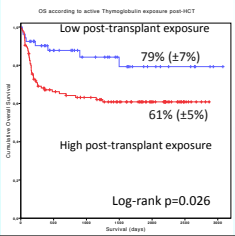
A) True
B) False

Conclusions

- A model was developed and validated, describing active Thymoglobulin® pharmacokinetics, yielding accurate predictions
- Weight and baseline lymphocytes important factors influencing the PK
- Current dosing regimen results in increasing exposure with higher weight
- First step in developing an individualized dosing regimen

Perspectives

- Pharmacokinetic-pharmacodynamic (concentration-effect) relationship needs to be explored
- Development of a dosing regimen to reach optimal exposure



Multivariate predictors for worse overall survival:
- *Post-HCT AUC >20, p=0.024*
- *Mismatched donor, p=0.01*
- *Malignancy, p=0.007*

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