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Individualized dosing of serotherapy in allogeneic hematopoietic cell transplantation - a delicate balance

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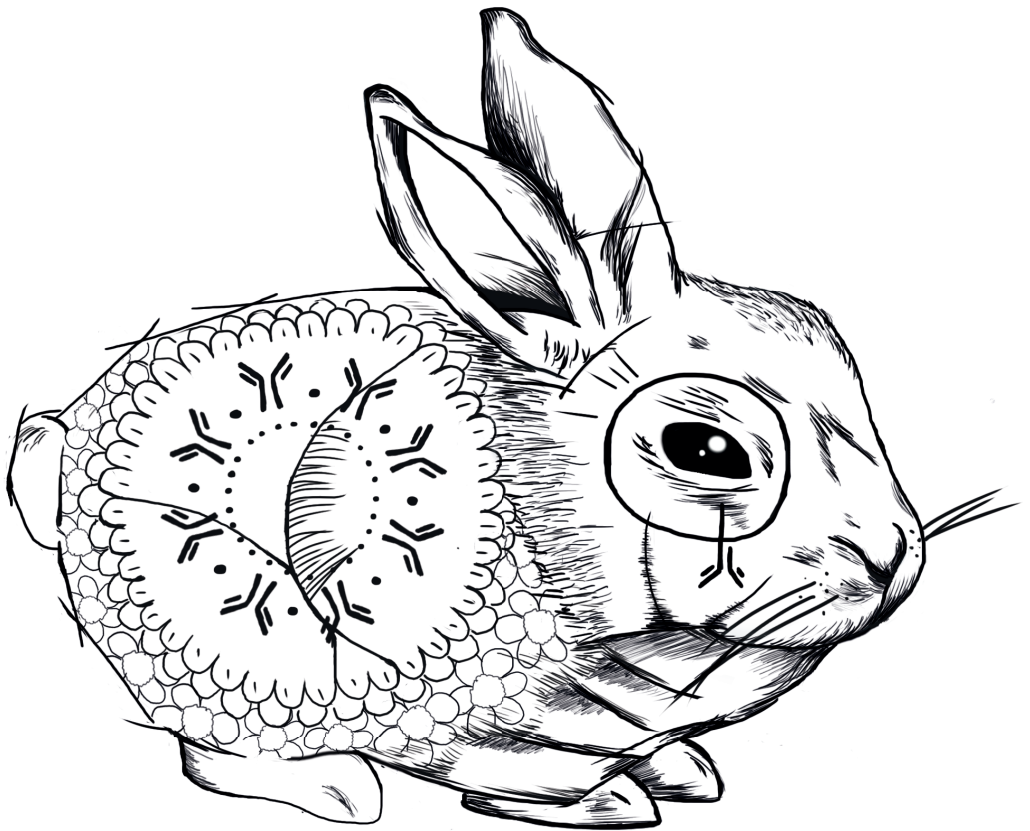


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Dankwoord/Acknowledgements

CURRICULUM VITAE

Rick Admiraal was born on February 1st 1984 in Beverwijk, the Netherlands. He attended secondary school at the Jac. P. Thijsseschool in Castricum where he graduated in 2002. That year, he started his medical studies at the University of Amsterdam. He did his research internship at the Department of Pediatric Oncology. As part of his clinical rotations, he did a 5-month elective internship in pediatric oncology at the Women's and Children's Hospital in Adelaide, Australia. After obtaining his medical degree in 2011, he worked as a resident at the department of pediatrics at Tergooi Ziekenhuizen in Blaricum. In 2012, he was appointed PhD-student at the University Medical Center Utrecht (UMCU), the Leiden Academic Centre for Drug Research (LACDR) and the Leiden University Medical Center (LUMC) under the supervision of prof. dr. Catherijne Knibbe, dr. Jaap Jan Boelens and dr. Robbert Bredius. His studies focus on individualized dosing of serotherapy in hematopoietic cell transplantation, and have resulted in this thesis. He received the best abstract award at the annual meeting of the American Society for Bone Marrow Transplantation in 2013 and 2015 (pharmacology) and at the International Cord Blood Symposium 2016. During his PhD, he was trained as a clinical pharmacologist in the UMC Utrecht. In his spare time, he volunteers at a sailing camp for children with cancer, where he later joined the board. He currently works as a resident pediatrics at the Meander Medisch Centrum in Amersfoort. From 2017, he starts his residency in pediatrics at the University Medical Center Utrecht. Rick lives in Amsterdam together with his partner Jacqueline van Gorp.

LIST OF PUBLICATIONS

Admiraal R, Nierkens S, de Witte MA, et al. Impact of exposure to anti-thymocyte globulin on survival chances following haematopoietic cell transplantation: a retrospective pharmacokinetic-pharmacodynamic analysis. *Lancet Haematology* 2017 epub

Admiraal R, de Koning CCH, Lindemans CA, et al. Viral Reactivations and Associated Outcomes in Context of Immune Reconstitution after Pediatric Hematopoietic Cell Transplantation. *Journal of Allergy and Clinical Immunology*. 2016 epub

Admiraal R, Lindemans CA, van Kesteren C, et al. Excellent T-cell reconstitution and survival provided ATG exposure is low or absent after pediatric cord blood transplantation. *Blood*. 2016; 128:2734-2741

Admiraal R, van Kesteren C, Nierkens S, Boelens JJ. Antithymocyte globulin: Importance of good clinical pharmacological practice. *Journal of Allergy and Clinical Immunology*. 2016;138:633

Admiraal R, Boelens JJ. Individualized conditioning regimes in cord blood transplantation: Towards improved and predictable safety and efficacy. *Expert Opinion in Biological Therapy*. 2016;2598:1-13.

Admiraal R, Chiesa R, Lindemans CA, et al. Leukemia-free survival in myeloid leukemia, but not in lymphoid leukemia, is predicted by early CD4+ reconstitution following unrelated cord blood transplantation in children: a multicenter retrospective cohort analysis. *Bone Marrow Transplantation*. 2016;73:1-3.

Admiraal R, van Kesteren C, Jol-van Der Zijde CM, et al. Association between anti-thymocyte globulin exposure and CD4+ immune reconstitution in paediatric haematopoietic cell transplantation: a multicentre , retrospective pharmacodynamic cohort analysis. *Lancet Haematology*. 2015;2(5):e194-e203.

Lindemans CA, te Boome LCJ, Admiraal R, et al. Sufficient Immunosuppression with Thymoglobulin Is Essential for a Successful Haplo-Myeloid Bridge in Haploidentical-Cord Blood Transplantation. *Biology of Blood and Marrow Transplantation*. 2015;21(10):1839-1845.

Willemsen L, Jol-van der Zijde CM, Admiraal R, et al. Impact of Serotherapy on Immune Reconstitution and Survival Outcomes After Stem Cell Transplantations in Children: Thymoglobulin Versus Alemtuzumab. *Biology of Blood and Marrow Transplantation*. 2015;21(3):473-482.

Admiraal R, van Kesteren C, Jol-van der Zijde CM, et al. Population pharmacokinetic modeling of Thymoglobulin® in children receiving allogeneic-hematopoietic cell transplantation (HCT): towards improved survival through individualized dosing. *Clinical Pharmacokinetics*. 2015;54(4):435-446.

Admiraal R, van Kesteren C, Boelens JJ, Bredius RGM, Tibboel D, Knibbe C a J. Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. *Archives of Disease in Childhood*. 2014;99(3):267-272.

Admiraal R, Van Der Paardt M, Kobes J, Kremer L, Bisogno G, Merks J. High-dose chemotherapy for children and young adults with stage IV rhabdomyosarcoma. *Cochrane Database for Systematic Reviews*. 2010;12.

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell Mediated Cytotoxicity
AdV	Adenovirus
AIC	Akaike Information Criterion
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoid Leukemia
AML	Acute Myeloid Leukemia
APC	Antigen-Presenting Cell
ATG	Anti-Thymocyte Globulin
AU	Arbitrary Unit
AUC	Area Under the Curve
BDE	Bodyweight-Dependent Exponent
BK	BK-virus
BLQ	Below the Limit of Quantification
BM	Bone Marrow
BMF	Bone Marrow Failure
Campath	Registered brand of alemtuzumab
CAR	Chimeric Antigen Receptor
CB	Cord Blood
CBT	Cordblood Transplantation
CD4+ IR	Immune reconstitution of CD4+ T-cells (T-helper cells)
CDC	Cell-Dependent Cytotoxicity
C _{graft}	Peri-transplant concentrations
C _{HCT}	Concentration at the time of HCT
CL	Clearance
CLL	Chronic Lymphoid Leukemia
C _{max}	Maximum Concentration
CMV	Cytomegalovirus
CsA	Cyclosporin A
CTL	Cytotoxic T-lymphocyte
CWRES	Conditional Weighted Residuals
DC	Dendritic Cell
EBV	Epstein-Barr Virus
EFS	Event-Free Survival
ELISA	Enzyme-Linked Immuno Sorbent Assay
EMA	European Medicines Agency

FDA	Food and Drug Administration
FOCE-I	First Order Conditional Estimation with Interaction
GF	Graft Failure
GOF	Goodness of Fit plots
GvHD	Graft-versus-Host-Disease
GvL	Graft-versus-Leukemia
HCT	Hematopoietic Cell Transplantation
HHV6	Human Herpes Virus 6
HLA	Human Leukocyte Antigen
HR	Hazards Ratio
iBW	Ideal Body Weight
IEM	Inborn Errors of Metabolism
IgG	Immunoglobulin G
IQR	Interquartile Range
IR	Immune Reconstitution
K_m	Michaelis-Menten constant
LBW	Lean Body Weight
MMF	Mycophenolate Mofetil
MMUD	Mismatched Unrelated Donor
MPS	Mucopolysaccharidosis
MRD	Minimal Residual Disease
MSD	Matched Sibling Donor
MUD	Matched Unrelated Donor
NONMEM	Non-Linear Mixed Effects Modeling (software)
NPDE	Normalized Prediction Distribution Errors
NRM	Non-Relapse Mortality
OFV	Objective Function Value
OR	Odds Ratio
OS	Overall Survival
PARACHUTE	Prospective trial to evaluate individualized ATG dosing
PBPK	Physiology-Based Pharmacokinetics
PBSC	Peripheral Blood Stem Cells
PD	Pharmacodynamics
PID	Primary Immune Deficiency
PIRCHES	predicted indirectly recognizable HLA epitope
PK	Pharmacokinetics
PsN	Pearl speaks NONMEM (software)
Q-FACS	Quantative Fluorescence-Activated Cell Sorting
RIC	Reduced Intensity Conditioning

RRM	Relapse-Related Mortality
TBI	Total Body Irradiation
TCR	T-cell Repertoire
TDM	Therapeutic Drug Monitoring
TGF	Tumor Growth Factor
Thymoglobulin	Brand of ATG
TMDD	Target-Mediated Drug Disposition
TNC	Total Nucleated Cells
V_1	Central volume of distribution
$V_{\max}$	Maximum elimination rate
VPC	Visual Predictive Check
WBC	White Blood Cell Count
WRES	Weighted Residuals

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