Prospective Analysis of an individualized dosing Regimen of ATG (Thymoglobulin) in Children Undergoing HCT: redUcing Toxicity and improving Efficacy * a single arm phase II study

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To investigate whether an individualized dosing regimen for Thymoglobulin leads to a better immune reconstitution after HCT (definition as in primary endpoint), as compared to historically non-individualized treated patients receiving Thymoglobulin...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON47267

Source
ToetsingOnline

Brief title
Parachute trial

Condition

- Leukaemias
- Immune system disorders congenital
- Immunodeficiency syndromes

Synonym
Individualised ATG dosing in standard of care in stem cell transplantion

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW,Sanofi Aventis,Sanofi-aventis

Intervention

Keyword: ATG, Children, Hematopoietic Cell Transplantation, Thymoglobulin

Outcome measures

Primary outcome

Incidence of CD4+ T-cell immune reconstitution, defined as a CD4+ T-cell count

> 50 x 10e6/L in 2 consecutive measurements within 100 days.

Secondary outcome

* Survival (overall survival, event free survival, non-relapse mortality,

relapse mortality)

* Relapse incidence

* Incidence of viral reactivations (CMV, Adenovirus, EBV, HHV6, BK-virus)

* Acute graft versus host disease (according to Glucksberg criteria)

* Chronic graft versus host disease (according to Shulman criteria)

* Engraftment defined as a neutrophil count > 0.5 x 109/L with use of

granulocyte-colony stimulating factor (G-CSF) within 40 days

* Rejection defined as >95% recipient chimerism, or reinfusion of donor cells

after successful engraftment

* Prospective validation of the pharmacokinetic model

* Lymphocyte subset reconstitution monitored throughout the treatment

(including some rare populations) for future studies

Study description

Background summary

Thymoglobulin® was introduced to the conditioning regimen in hematopoietic cell transplantation (HCT) to prevent graft-versus-host-disease (GvHD) and graft failure. Side effects of Thymoglobulin® include delayed immune reconstitution (IR) of donor T-cells due to its long half-life and potential remaining circulating drug post-HCT resulting in an increased probability of viral reactivations/infections. The currently used dosing regimen for Thymoglobulin in children, comprising of 2.5 mg/kg IV once daily x 4 days, usually from day -5 prior to transplantation leads to markedly different exposures across the pediatric age range. Also the peripheral blood lymphocyte count at the first dose of Thymoglobulin is a variable influencing pharmacokinetics which is currently not taken into account. In a retrospective analysis, low post-HCT Thymoglobulin AUC was associated with a high chance on successful IR, defined as a CD4+ T-cell count >50 x 10e6/L in 2 consecutive measurements within 100 days. This count was chosen based on literature, where counts under this limit are associated with a higher probability of viral reactivations. Currently, 60% of patients reach this criterion of immune-reconstitution (HCT*s in Utrecht and Leiden from 2004-2012, n=260), which is associated with a lower incidence of relapse- and non-relapse mortality.
Low pre-HCT exposure on the other hand was associated with reduced GvHD and rejection. Using the optimal exposure combined with the PK-model, we developed an individual dosing regimen for Thymoglobulin, aiming for improved IR and a reduction of GvHD and graft failure. The goal of this study is to investigate the effects of an individualized PK/PD based dosing regimen for Thymoglobulin on immune reconstitution after HCT.

Study objective

To investigate whether an individualized dosing regimen for Thymoglobulin leads to a better immune reconstitution after HCT (definition as in primary endpoint), as compared to historically non-individualized treated patients receiving Thymoglobulin as a fixed dose per kilogram body weight. The individualized dosing regimen is based on a previously treated pediatric cohort on which a population PK-PD analysis was performed. The dosing regimen was compiled using this cohort, taking into account the influence of body weight and pre-Thymoglobulin lymphocyte count and the observed variability.

Study design

Interventional, phase II, open label, clinical trial using historical controls

Intervention

Patients receive an individualized dose of Thymoglobulin according to a PK/PD derived dosing regimen as opposed to a fixed standard dose of 10 mg/kg Thymoglobulin, the current standard of care.

Study burden and risks

The risks of this study include inadequate treatment by too low Thymoglobulin exposure or overtreatment by a too high exposure. This can contribute to a higher incidence of HCT-related complications such as acute and chronic GvHD and graft failure, or delayed or absent immune reconstitution, in low and high exposure respectively. Possible benefit of this study is better controlled Thymoglobulin serum levels, including lower post-HCT Thymoglobulin exposure, leading to improved immune reconstitution, and an increase in pre-HCT exposure aimed to prevent GvHD and graft failure. If applicable, the above-mentioned complications will be treated according to the current standardized treatment SOPs for GvHD and viral reactivations.
This study will be conducted in pediatric patients, as there are significant changes in pharmacokinetics in this population, which are not implemented in current guidelines. This leads to markedly differing exposure, being associated with treatment outcome.

The burden for patients in this study involves blood samples taken from an existing central line (n=1-7, depending on number of doses of Thymoglobulin, 1-3 ml per sample). Follow-up and assessment of endpoints are performed according to the standard HCT care and therefore do not impose an additional burden.

Contacts

Public
Dutch Childhood Oncology Consortium Early Clinical Trial Center

Lundlaan 6
Utrecht 3512 LJ
NL
Scientific
Dutch Childhood Oncology Consortium Early Clinical Trial Center

Lundlaan 6
Utrecht 3512 LJ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* All patients eligible for a non-haplo-identical non-T-cell depleted HCT with Thymoglobulin as part of the conditioning regimen treated in the pediatric ward of the UMCU Utrecht or the LUMC Leiden
* Any stem cell source
* First transplantation
* Age at time of transplantation < 18 years
* Signed written informed consent according to local law and regulations
* Lansky/Karnofsky * 80%

Exclusion criteria

* Withdrawal of or no informed consent
* No Thymoglobuline in conditioning regimen
* Lansky / Karnofsky <80%
* Ex-vivo T-cell depleted grafts
* Other serotherapy in conditioning (e.g. campath, or campath in the bag)
* Received serotherapy within 3 months before this transplantation
* Pregnancy
* Sensibility to rabbit proteins or previous treatment with Thymoglobulin
* Acute or chronic infections, in which each form of immune suppression is contra-indicated
* Patients not receiving the full intentioned dose of Thymoglobulin due to any reason
* Cardiac ejection fraction < 30%
* No complete remission (CR-status) in case of malignancy
* History of serious immune-mediated reactions or hypersensitivity to any biological product
* Participation in other trial in which the dose of Thymoglobulin is fixed to amounts other than the individualized dose.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-06-2015
Enrollment:	53
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Thymoglobulin
Generic name:	Anti-Thymocyte Globulin (Rabbit) - ATG
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-02-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-12-2018

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26849
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-004849-26-NL
CCMO	NL51460.041.14
OMON	NL-OMON26849