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

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26849

Source
NTR

Brief title
PARACHUTE-trial

Health condition

Bone Marrow Transplantation
Stem cell transplantation
Thymoglobulin
ATG
Thymoglobuline
Beenmergtransplantatie
Stamceltransplantatie
Immuunreconstitutie
Immune Reconstitution

Sponsors and support

Primary sponsor: UMC Utrecht

Source(s) of monetary or material Support: Sanofi Aventis, France
ZonMW, NWO, The Netherlands

Intervention

Outcome measures

Primary outcome

Incidence of CD4+ T-cell immune reconstitution, defined as a CD4+ T- cell count > 50 x 106/L in 2 consecutive measurements within 100 days.

Secondary outcome

• Survival (overall survival, event free survival, non-relapse mortality, relapse mortality) at 1 year follow-up

• Relapse incidence at 1 year follow-up

• Incidence of viral reactivations (CMV, Adenovirus, EBV, HHV6, BK-virus) at 1 year follow-up

• Acute graft versus host disease (according to Glucksberg criteria3)

• Chronic graft versus host disease (according to NIH criteria4) at 1 year follow-up

• 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 at 1 year follow-up

• 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 leads to markedly different exposures across the pediatric age range. Low post-HCT Thymoglobulin AUC is associated with a high chance on successful immune reconstitution, important for preventing viral reactivations and relapse. High pre-HCT exposure on the other hand led to a decrease in GvHD and rejection.We defined an optimal exposure based on historical data with which a PK-model was generated, and developed an individual dosing regimen for Thymoglobulin, aiming for improved IR and a reduction of GvHD and graft failure. The goal of this prospective study is to investigate the effects of an individualized PK/PD based dosing regimen for Thymoglobulin on immune reconstitution after pediatric HCT.

Study objective

Our hypothesis is that individualized dosing of Thymoglobulin will result in an improved immune reconstitution, without significantly increasing the risk on aGvHD. This may lead to an improved survival, both through reducing non-relapse mortality (GvHD, viral reactivations) as well as relapse mortality. As a final step in the validation process of our proposed individualized dosing strategy, this needs to be studied in in a prospective, phase II trial.

Study design

Primary endpoints will be assessed at 100 days post-HCT, engraftment at 40 days post-HCT, other endpoints at 1 year follow up

Intervention

Patient will 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.

Contacts

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Eligibility criteria

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 participating centers

- Any hematopoietic stem cell source

- First transplantation

- Age at time of transplantation (i.e. infusion of stem cells) < 18 years

- Signed written informed consent according to local law and regulations

- Lansky/Karnofsky ≥ 70%

Exclusion criteria

- 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 or breast-feeding or unwilling to use adequate contraceptive methods

- 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 planned to receive or having received at least 90% intentioned dose of

Thymoglobulin

- Ejection fraction < 30%

- No complete morphological remission (CR-status) in bone marrow in case of malignancy

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2015
Enrollment:	53
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	27-01-2015
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47267
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL4836
NTR-old	NTR4960
CCMO	NL51460.041.14
OMON	NL-OMON47267

Study results

Summary results
Admiraal et al, Clinical Pharmacokinetics 2014
Admiraal et al, Lancet Haematology 2015.