Impact of Alemtuzumab exposure on immune reconstitution, autoimmunity, risk of infection, chimerism and Graft-versus-Host Disease in children with non-malignant diseases undergoing allogeneic stem cell transplantation. ARTIC International Multicenter Observational Study.

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Primary objectiveTo evaluate current clinical practice and develop a population based Campath® (Alemtuzumab) pharmacokinetics model for predicting total Alemtuzumab exposure after i.v. administration before allogeneic stem cell transplantation in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Haemoglobinopathies
Study type	Observational non invasive

Summary

ID

NL-OMON55607

Source
ToetsingOnline

Brief title
ARTIC study

Condition

- Haemoglobinopathies
- Immune system disorders congenital

- Immunodeficiency syndromes

Synonym
Group of inherited blood diseases that affect red blood cells (e.g. sickle cell disease, thalassemia) and/or white blood cells (e.g. severe combined immunodeficiency characterized by a profound reduction or absence of T lymphocyte function) requiring an allogeneic stem cell transplantation.

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Leiden University Medical Center;The Netherlands; Children□s Research Center of Zurich;Switzerland; private charitable foundations (Wolfermann-Nägeli private foundation;Zurich;Switzerland; Aldo e Cele Daccò private foundation;Lugano;Switzerland;EMDO private foundation;Zurich;Switzerland).

Intervention

Keyword: - Campath/Alemtuzumab, - Graft-versus-host disease, - Immune recovery, - Pharmacokinetics/pharmacodynamics

Outcome measures

Primary outcome

Campath® (Alemtuzumab) levels measured 15-30 minutes before (please note: no

sample will be taken before the first Alemtuzumab dose) and after each Campath®

(Alemtuzumab) administration as well as at day 0 (= day HSCT), +1, +7, +14, +21

and at week +4 and +6 after alloHSCT.

Secondary outcome

Explorative secondary Endpoints (outcome parameters)

• Immune reconstitution:

-- Lymphocytes / neutrophils / monocytes / T cells (total, CD4+ and CD8+

subsets, CD4+/CD8+ ratio) / NK cells / B cells count are measured at week +2

(if peripheral leucocytes are measurable yet), +3, +4, +6, +8, +10 and +12

after alloHSCT;

-- Neutrophil (CD15+ cells) engraftment

-- Recovery of CD4+ T cells

-- Recovery of CD8+ T cells

- Chimerism analysis of total peripheral blood mononuclear cells (PBMC) at week +4, +8, +12 and at +6, +9 and +12 months after alloHSCT;

• Incidence of acute and chronic graft-versus-host-disease (GvHD) and grading according to classic Glucksberg-Seattle scale and NIH criteria respectively;

• Overall survival (OS);

• Event free survival (defined as without death or retransplantation);

• Cumulative incidence of treatment-related mortality (TRM);

• Cumulative incidence of graft failure (defined as non-engraftment or rejection);

• Incidence of viral primary infections or reactivations (e.g. cytomegalovirus, Epstein-Barr-virus, human herpesvirus 6, adenovirus) within the first 100 days;

• Incidence of Donor Lymphocyte Infusion (DLI) within the first 100 days;

• Incidence of bacterial, parasitic and fungal primary infections within the first 100 days;

• Incidence of autoimmune reactions (e.g. autoimmune cytopenia, autoimmune haemolytic anemia) within 10 years after alloHSCT (serum samples will be taken if indicated);

• Incidence of secondary immune-mediated endocrine disorders (e.g. gonadal dysfunction, hypothyreosis).

Study description

Background summary

Children with severe congenital immunological and non-malignant hematological disorders (e.g. primary immunodeficiencies and hemoglobinopathies) have a poor quality of life and a markedly reduced life expectancy. They carry a huge health economic burden due to frequent hospitalization, progressive organ damage and disabilities that tend to increase during adolescence and adulthood with major socio-economic implications on the affected patients, their families, and on the society. Despite a variable clinical course, feasible systematic transfusion program and infection prophylaxis, many patients develop life-threatening infections and end-organ complications. For these patients allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the only established curative treatment aiming at reconstitution of healthy donor-type immuno- and hematopoiesis. Early transplant related morbidity and mortality due to severe infections, graft failure and graft-versus-host-disease (GvHD) remain serious complications of this otherwise curative therapy modality.

Campath® (Alemtuzumab) is a humanized IgG monoclonal antibody targeting the CD52-antigen, a membrane protein expressed on the surface of several peripheral blood immune cells (e.g. B cells, monocytes, NK cells) and in particular on T-lymphocytes, but not on hematopoietic stem cells. Prior to alloHSCT, Campath is prescribed to eliminate a.o. T-cells, thereby preventing GvHD and graft rejection. However, Campath® (Alemtuzumab) persistence in blood usually causes a prolonged immune depletion and a delayed immune recovery, thereby increasing the risk of infection and autoimmune reactions.

In children, Campath® is considered standard of care prior to alloHSCT (off-label use) following the recommendation of the European Society for Blood and Marrow Transplantation and of the European Society for Immunodeficiencies as well as according to relevant peer-reviewed literature.
Recent publications on pediatric Campath® (Alemtuzumab) pharmacokinetics (PK) suggest large inter-patient variability and consequent repetitive overdosing, thus significantly impacting biological efficacy and clinical outcome. However, neither the proper identification of Campath® (Alemtuzumab) PK determinants nor an accurate evaluation of the current (reduced) Campath® dose recommendation of 0.4-1.0mg/kg was possible up to now.

Primary hypothesis
High interindividual variability of Campath® (Alemtuzumab) PK in children transplanted for severe non-malignant diseases crucially impacts the cumulative exposure to Alemtuzumab given intravenously as part of a treosulfan- or busulfan-based reduced intensity conditioning (RIC) regimen pre and post alloHSCT.

Secondary Hypothesis
The exposure to Campath® (Alemtuzumab) correlates significantly with immune reconstitution, risk of acute and chronic GvHD and primary clinical outcome defined as incidence of infectious complications, reactive autoimmunity and secondary immune-endocrine disorders in children with non-malignant diseases undergoing alloHSCT.

Study objective

Primary objective
To evaluate current clinical practice and develop a population based Campath® (Alemtuzumab) pharmacokinetics model for predicting total Alemtuzumab exposure after i.v. administration before allogeneic stem cell transplantation in children with non-malignant diseases treated with treosulfan- or busulfan-based reduced intensity conditioning regimens.

Secondary objectives
• To evaluate whether variation in exposure to Campath® (Alemtuzumab) correlates significantly with immune reconstitution, mixed chimerism incidence as well as acute and chronic GvHD incidence and grade.
• To investigate whether variation in Alemtuzumab exposure correlates significantly with the incidence of infectious complications, autoimmune reactions and secondary immune-endocrine disorders.

Study design

International multicenter observational study.

Study burden and risks

Our observational study focuses on children with congenital severe immunological or haematological disorders prior to stem cell transplantation and, therefore, on vulnerable participants. Considering the severe clinical course and prognosis of these particular primary diseases that our study is analysing, no adult cohort could be eligible for this clinical research.

Children with congenital severe immunological or haematological disorders carry the heaviest burden of disease and without definitive treatment, the condition is mostly fatal. Allogeneic hematopoietic stem cell transplantation is an extremely effective way of restoring the immuno- and hematopoiesis, but a high level of expertise and innovative individualized treatment approaches available at all participating centers are mandatory.

In this study, the impact of Campath® (Alemtuzumab) on clinical outcome in children will be accurately investigated providing fundamental data for precise dosing recommendations, thereby allowing further crucial therapeutic

improvements to benefit future patients. To protect our study participants, this observational study will be conducted at national reference centers for pediatric immune-hematological disorders. Only investigators and medical personal who are experienced in working with children will be directly involved in patients care.

Special attention was accorded to the schedule of assessments to minimize burden and time effort for participants. Patients care, comprehension of informed consent and voluntary participation will be of high priority. The study will neither extend the duration of the hospitalisation nor increase the frequency of consultations on the outpatient clinic. Since a central venous line is mandatory for stem cell transplantation, the blood samples collection will be pain- and stress-less and only performed by experienced pediatric nurses to minimize the risk of complications (e.g. infections). The extra collection of a limited number (5 to maximal 9) of blood samples for pharmacokinetics analyses may eventually lead to a slightly increased risk of developing a central venous line infection. However, we consider this risk to be very low.
The risk of unauthorized data access and/or unwanted identification of project participants will be assured.

We conclude that the potential benefit of our observational study far outweighs the possible risks of our additional measurements.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• diagnosis of severe congenital immune deficiency or of congenital hematological disorder with an indication for HSCT, e.g. (severe) combined immunodeficiency ((S)CID), hemophagocytic lymphohistiocytosis (HLH), chronic granulomatous disease (CGD), thalassemia major, sickle cell disease (SCD);
• age at diagnosis and at the time of HSCT <= 18 years;
• Alemtuzumab treatment intravenously (iv) is given as part of a treosulfan- or a busulfan-based reduced intensity conditioning regimen prior to alloHSCT;
• all donor types and hematopoietic stem cell sources will be considered;
• allogeneic hematopoietic stem cell transplantation is performed in a study participating center; written consent of the parents (legal guardian) and of the patient herself or himself if >=14 years old (>=12 years old in the Netherlands);
• in case of multiple alloHSCT per patient, further transplantations will only be considered if a minimal serotherapy-free interval of 3 months is preceding the second transplant

Exclusion criteria

• patients who do not fulfill the inclusion criteria;
• patients with known hypersensitivity to Alemtuzumab;
• patients treated with other serotherapy drugs (e.g. anti-thymocyte globulin - ATG) within the same conditioning regimen prior to HSCT;
• patients who received any other serotherapy in the last 3 months before starting this observational study;
• known HIV-positivity;
• severe uncontrolled infections before alloHSCT;
• active malignancies;
• pregnancy/lactation.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-03-2020
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	22-11-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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: 22218
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL68506.058.19

Study results

Date completed:	31-12-2022
Results posted:	09-05-2023
Actual enrolment:	7

First publication
04-04-2023