PK/PD of corticosteroids in graft-versus-host disease after hematopoietic cell transplantation in children

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To assess the PK/PD relationship of prednisolone as either prophylaxis or therapy of GVHD in children after HCT.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	-
Study type	Observational invasive

Summary

ID

NL-OMON21503

Source
Nationaal Trial Register

Brief title
PIKACHU

Synonym
Pharmacokinetics; Pharmacodynamics; Population PK/PD; Graft-versus-host disease; Prednisolone

Health condition

Graft versus host disease after hemotopoetic cell transplantation

Research involving
Human

Sponsors and support

Primary sponsor:	Prinses Maxima Centrum
Secondary sponsors:	Universitair Medisch Centrum Utrecht
Source(s) of monetary or	Harmannus Ehrhardt Stichting

material Support:

Intervention

- Medicine

Explanation

Outcome measures

Primary outcome

PK parameters of prednisolone as either prophylaxis or therapy of GVHD in children after HCT will be assessed, even as other determinants for development of a population PK model using non-linear mixed effect modelling NON-MEM.

Secondary outcome

Exposure to corticosteroids as measured by area-under-the-curve (AUC), maximum concentration (Cmax), minimum concentration (Cmin) and time-above-threshold will be related to treatment outcome. Treatment outcome is defined as occurrence and grade of GVHD in case of prophylactic therapy and defined as the need for escalation of therapy for treatment of GVHD. Biomarkers will be assessed using cell (mostly flowcytometry) and protein (Luminex and Olink) assays.

Study description

Background summary

Rationale: One of the biggest obstacles in allogeneic hematopoietic cell transplantation (HCT) remains the development of graft-versus-host disease (GVHD), which occurs in approximately 40% of stem cell recipients. First-line treatment to either prevent or treat GVHD is high dose systemic corticosteroids. However, the incidence of the development of GVHD in children receiving corticosteroids as prophylactic treatment is still high. Besides, only a minority of the patients developing GVHD responds adequately to corticosteroid treatment, often with lifelong therapy and reduced quality of life. Overall mortality after developing GVHD is around 30%. In current clinical practice, corticosteroid dosing is highly empirical and might result in very variable exposure levels in children. We hypothesize that precision dosing of corticosteroids, to reach an optimal exposure in every individual patient, will increase response rates in pediatric HCT. A pharmacokinetic/pharmacodynamic (PK/PD) relationship of corticosteroids has been suggested in other diseases where exposure to corticosteroids is associated with clinical outcomes. To date, this has not yet been investigated in the setting of GVHD. As a first step to optimize therapy for GVHD, we will study the PK/PD relationship of prednisolone in pediatric patients. If such a relationship exists, optimal dosing strategies can

be developed. Objective: To assess the PK/PD relationship of prednisolone as either prophylaxis or therapy of GVHD in children after HCT. Study design: Prospective observational study. Study population: All patients (aged 0-18 years, plus occasionally adolescents/young adults) treated by the Princess Máxima Center (PMC) with either prednisolone as prophylaxis or therapy for GVHD after HCT. Main study parameters/endpoints: Pharmacokinetic parameters and its associated variability of prednisolone and other determinants for the population PK model will be assessed using non-linear mixed effect modelling (NON-MEM). Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will not have direct benefit from participating in this study. The data obtained in this study will be used to assess the population PK and PD of prednisolone in children after HCT. Burden will be minimal since for pharmacokinetics 4 to 5 (additional to SOC) blood samples of 2 ml once or twice will be drawn (limited sampling strategy) and any samples possible of 9 ml to study biomarkers. The volume of blood that is drawn for the study does not exceed the recommended maximum. The applied sampling strategy is minimally invasive, since all the patients that are included already have a central line. Sampling will only be requested during hospitalization after HCT and/or development of GVHD.

Study objective

To assess the PK/PD relationship of prednisolone as either prophylaxis or therapy of GVHD in children after HCT.

Study design

Prospective observational study.

Primary: PK parameters of prednisolone as either prophylaxis or therapy of GVHD in children after HCT will be assessed, even as other determinants for development of a population PK model using non-linear mixed effect modelling (NON-MEM).

Secondary: Exposure to prednisolone as measured by area-under-the-curve (AUC), maximum concentration (Cmax) or time-above-threshold will be related to treatment outcome. Treatment outcome is defined as occurrence and grade of GVHD in case of prophylactic therapy and defined as the need for escalation of therapy for treatment of GVHD. Biomarkers will be assessed using cell (mostly flowcytometry) and protein (Luminex and Olink) assays.

Intervention

No intervention in the standard of care. This is an observational study.

Study burden and risks

One of the biggest obstacles in hematopoietic cell transplantation (HCT) remains the development of graft-versus-host disease (GVHD), which occurs in approximately 40% of stem cell recipients. First-line treatment to either prevent or treat GVHD is high dose

systemic corticosteroids. However, the incidence of the development of GVHD in children receiving corticosteroids as prophylactic treatment is still high. Besides, only a minority of the patients developing GVHD responds adequately to corticosteroid treatment, often with life long therapy and reduced quality of life. Overall mortality after developing GVHD is around 30%. In current clinical practice, corticosteroid dosing is highly empirical and might result in very variable exposure levels in children. We hypothesize that precision dosing of corticosteroids, to reach an optimal exposure in every individual patient, will increase response rates in pediatric HCT. A pharmacokinetic/pharmacodynamic (PK/PD) relationship of corticosteroids has been suggested in other diseases where exposure to corticosteroids is associated with clinical outcomes. To date, this has not yet been investigated in the setting of GVHD. As a first step to optimize therapy for GVHD, we will study the PK/PD relationship of prednisolone in pediatric patients. If such relationship exists, optimal dosing strategies can be developed.

Contacts

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Eligibility criteria

Age
Newborns
Newborns
Babies and toddlers (28 days-23 months)
Babies and toddlers (28 days-23 months)
Children (2-11 years)
Children (2-11 years)
Adolescents (12-15 years)
Adolescents (12-15 years)
Adolescents (16-17 years)
Adolescents (16-17 years)
Adults (18-64 years)
Adults (18-64 years)

Inclusion criteria

1. Patients treated by the PMC; 2. Planned to receive systemic corticosteroids after HCT; 3. Informed consent form (ICF) signed prior to participation in the study; 4. A present central line to sample blood

Exclusion criteria

None in advance. However, according to expert opinion of the PI, any disease/circumstance that may influence the participation of the potential subject in a negative way, will be excluded from participation in this study.

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2020
Enrollment:	130
Type:	Actual

IPD sharing statement

Plan to share IPD: Yes

Plan description
Data from the population pharmacokinetics, the PK-PD model and any optimized dosing

recommendations will be published and shared with the relevant profession through articles, poster presentations, etc.

Ethics review

Approved WMO
Date: 12-06-2020

Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 54530
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8703
CCMO	NL70886.041.19
OMON	NL-OMON54530

Study results

Summary results
Not applicable