PHASE I/II CLINICAL TRIAL OF AUTOLOGOUS HEMATOPOIETIC STEM CELL GENE THERAPY FOR RAG1-DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY

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This study has been transitioned to CTIS with ID 2023-510204-50-00 check the CTIS register for the current data. Primary: The main objectives of the study are to demonstrate feasibility and safety of gene corrected autologous CD34+-selected...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON54570

Source
ToetsingOnline

Brief title
Phase I/II clinical trial on RAG1 gene therapy in SCID

Condition

- Immunodeficiency syndromes

Synonym
RAG1 SCID; severe combined immunodeficiency

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw,EU-H2020

Intervention

Keyword: Gene therapy, RAG1, SCID

Outcome measures

Primary outcome

The primary endpoints are feasibility based on the successful generation of an IMP meeting the release criteria for administration to RAG1 deficient SCID patients, and safety based on event free survival (EFS) after infusion of the IMP with events defined as a) infusion of unmanipulated backup stem cell product and/or allogeneic HSCT because of failure of hematological and/or immunological reconstitution after RAG1 LV cell infusion and b) occurrence of insertional mutagenesis presenting as malignant disease.

Secondary outcome

Secondary endpoints are a) overall survival, b) efficacy by determining T cell reconstitution (CD3 T cells > 300/µL blood), thymic function (presence of naïve CD4 T cells) and T and B cell receptor molecular repertoire at one year and immunoglobulin substitution dependence at two years after infusion of the RAG1 LV CD34+ cells, and vector copy numbers in leukocyte subpopulations at one year, and c) clinical outcome by determining the rate of infections, recovery from failure to thrive, and quality of life.

Study description

Background summary

Severe combined immunodeficiency (SCID) is a genetically heterogeneous life-threatening disease characterized by severely impaired T cell development with or without impaired NK and B cell development or function depending on the genetic defect. Mutations in recombination activating genes 1 and 2 (RAG1 and RAG2) represent about 20% of all types of SCID. SCID is a paediatric emergency since it leads to severe and recurrent infections often in combination with protracted diarrhoea and failure to thrive. When left untreated, it is usually fatal within the first year of life. Currently, the only curative treatment option for RAG deficient SCID is allogeneic hematopoietic stem cell transplantation (HSCT). Despite improvements in HSCT in recent years, this treatment is associated with serious potential complications like graft-versus-host disease which results in an unfavourable outcome, particularly in patients who lack a human leukocyte antigen (HLA)-matched donor. In recent years, gene therapy based on transplantation of autologous gene-corrected hematopoietic stem cells (HSC) has evolved as an effective and safe therapeutic option for X-linked and ADA-deficient forms of SCID. We have recently demonstrated that gene therapy using lentiviral self-inactivating (SIN) vectors expressing codon-optimized human RAG1 in a mouse model for RAG1-deficient SCID effectively restores T and B cell development and function. In this phase I/II explorative intervention study feasibility, safety and efficacy of gene therapy using gene corrected autologous CD34+-selected mobilized peripheral blood or bone marrow cells will be investigated in patients with RAG1-deficient SCID with an indication for allogeneic HSCT but lacking a HLA-matched donor.

Study objective

This study has been transitioned to CTIS with ID 2023-510204-50-00 check the CTIS register for the current data.

Primary: The main objectives of the study are to demonstrate feasibility and safety of gene corrected autologous CD34+-selected hematopoietic stem cell therapy using a lentiviral SIN vector encoding codon-optimized human RAG1 cDNA in patients with RAG1-deficient SCID.

Secondary: To demonstrate efficacy of this therapeutic intervention based on a) T and B cell reconstitution at one year after infusion of the investigational medicinal product, b) persistence of gene marking in myeloid and lymphoid cell lineages in blood and marrow, and c) recovery from failure-to-thrive and/or serious/invasive infections

Study design

This study is a prospective, non-randomized, explorative open label, multicenter phase I/II intervention study designed to treat children up to 24 months of age with RAG1-deficient SCID with an indication for allogeneic hematopoietic stem cell transplantation but lacking a HLA-matched donor. The study involves infusion of autologous CD34+ cells transduced with the pCCL.MND.coRAG1.wrpe lentiviral vector (hereafter called RAG1 LV CD34+ cells) in ten patients with RAG1-deficient SCID.

Intervention

Patients will receive a single infusion of autologous CD34+ hematopoietic stem cells transduced with the pCCL.MND.coRAG1.wrpe lentiviral vector (RAG1 LV CD34+ cells).

Study burden and risks

The study focuses on feasibility, safety and efficacy of gene therapy using corrected autologous HSC in RAG1-deficient SCID patients. Based on results from other gene transfer studies and our own experience, the infusion of cultured and gene altered autologous blood progenitors does not appear to be associated with any significant transfusion reactions and is expected to be less toxic to what can be expected in allogeneic SCT, the current standard of care. The risk and side effects associated with the use of chemotherapy conditioning prior to infusion of the autologous gene-corrected cells is similar or even less compared to the setting of allogeneic HSCT since less intensive conditioning will be used. The significant risk of graft versus host disease (GvHD) associated with standard allogeneic HSCT (20-25%) will be eliminated in this study with autologous cells. The expected duration of hospital admission, the frequency of blood sampling and the expected visits to the outpatient clinic after discharge are similar to the standard post HSCT procedures. Within the first year after infusion of the RAG1 LV CD34+ cells, two bone marrow aspirations will be performed under general anesthesia to assess engraftment of the infused IMP. When possible, these procedures will be combined with routine procedures, e.g. removal of a central venous access. Insertional mutagenesis remains a finite risk of gene therapy treatment using integrating vectors. However, recent work has shown that next generation vectors, particularly SIN vectors as used in this study, significantly reduce the incidence of insertional mutagenesis and so far, no malignant transformation has been reported in recent clinical trials including more than 100 patients using these SIN vectors. Even lentiviral-based gene therapy includes a potential risk for insertion mutagenesis. In contrast to the first-generation retroviral vectors, the occurrence of insertional mutagenesis when using SIN lentiviral vectors (> 250 patients), including the lentiviral vector versions used in our study, has so far been limited to a single case. Of note, the concerned a patient with a

completely different underlying disease compared to our study. The expected benefit of successful gene therapy involves restoration of humoral and cellular immunity without concomitant risk of GvHD, and as a consequence improved quality of life.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)

Inclusion criteria

- RAG1 deficient SCID as confirmed by genetic analysis
- Peripheral blood T cells < 300/µL and/or naïve T cells < 1/µL
- lack of an available HLA-matched donor (i.c. HLA-identical sibling or 10/10 (A, B, C, DR, DQ) allele-matched (un)related donor)
- Age < 2 years
- Age at least 8 weeks by the time of busulfan and fludarabine administration
- Signed consent form (parental or guardian)

- Able to return to the local HSCT centre for follow-up (per protocol) during the 2-year study and the 15 year long-term off study review

Exclusion criteria

- availability of a HLA-matched donor (i.c. HLA-identical sibling or 10/10 (A, B, C, DR, DQ) allele-matched (un)related donor)
- RAG 1 deficiency with peripheral blood T cells > 300/µL and/or naïve T cells > 1/µL
- Previous allogeneic stem cell transplantation
- Significant organ dysfunction/co-morbidity (including but not limited to the ones listed below)
a. Mechanical ventilation
b. Shortening fraction on echocardiogram <25%
c. Renal failure defined as dialysis dependence
d. Uncontrolled seizure disorder

- Omenn syndrome
- Any other condition that the investigator considers is a contraindication to collection and/or infusion of transduced cells for that individual or indicate patient's inability to follow the protocol, for example contraindication f to busulfan, major congenital abnormalities, ineligible to receive anaesthesia, or documented refusal or inability of the family to return for scheduled visits.
- Human immunodeficiency virus (HIV) infection or Human T-ceel Leukemia Virus (HTLV) infection).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-07-2021
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	25-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-09-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-510204-50-00
EudraCT	EUCTR2019-002343-14-NL

Register	ID
ClinicalTrials.gov	NCT-04797260
CCMO	NL70818.000.19