Treatment of chemo-refractory viral infections after allogeneic stem cell transplantation with multispecific T cells against CMV, EBV and AdV: A phase III, prospective, multicentre clinical trial

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This study has been transitioned to CTIS with ID 2024-512321-84-00 check the CTIS register for the current data. Primary objectives:Evaluation of efficacy of multispecific T-cell transfer in patients with chemo-refractory viral infections after...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON54824

Source
ToetsingOnline

Brief title
TRACE

Condition

- Viral infectious disorders

Synonym
virus diseases, virus infections

Research involving
Human

Sponsors and support

Primary sponsor: Klinikum der Universität München
Source(s) of monetary or material Support: European Union;Horizon 2020.

Intervention

Keyword: AdV, allogeneic stem cell transplantation, chemo-refractory viral infections, CMV, EBV, multispecific T cells, TRACE

Outcome measures

Primary outcome

Percentage of patients with viral clearance (defined as two consecutive

negative PCRs)

Percentage of patients with progression between Day 7 and Week 8 after T-cell

transfer

Secondary outcome

Incidence/severity of acute GvHD >= grade II until Week 8 and Week 15.

Incidence of newly occurring acute GvHD grade I from Day 0 to Week 8 and Week

15.

Incidence of chronic GvHD from Day 7 to Week 8 and to Week 15 after T-cell

transfer.

Time to newly occurring acute and chronic GvHD.

Acute toxicity: maximum toxicity on the day of T-cell transfer evaluated by

measuring vital signs prior to and at different times after the T-cell transfer

and monitoring of specific adverse events (chills, nausea, vomiting, diarrhoea,

abdominal pain, allergic reactions, respiratory dysfunction or headache from 1 hour prior to T-cell transfer to 4 hours post infusion).

Change in viral load of underlying viral infection as assessed by quantitative PCR analysis of peripheral blood; samples taken weekly from Day 7 to Week 8 after T-cell transfer as compared to samples taken at Day 0.
Time to 1 log change in viral load.
Percentage of patients with >=1 log decrease in CMV, EBV or AdV viral load at Week 8.
Number of reactivations of the underlying viral infection following initial viral clearance until end of follow-up.

Number of patients with reduction or clearance of clinical symptoms of underlyingviral infection from Day 7 to Week 8 after T-cell transfer as compared to Day 0.

Overall survival rate (OS): From Day 0 to end of follow-up.

Number of days requiring antiviral chemotherapy after T-cell transfer from Day 7 to Week 8 after T-cell transfer.
Time to last administration of defined antiviral medication or switch to prophylactic treatment from Day 0 to Week 8 after T-cell transfer.

Number of new viral reactivations (CMV, AdV or EBV) other than the underlying

viral infection per patient as assessed by PCR analysis and clinical symptoms throughout the study.

Number of days hospitalized after T-cell transfer from Day 7 to Week 8.

EQ-5D and FACT-BMT for adult patients (>=18 years), and PEDS-QL for paediatric patients (<18 years) at Screening and Week 8.

T-cell phenotyping, samples taken at Screening, Day 0 and each visit from Day 7 to Week 15 after T-cell transfer.
Analysis of virus-specific T cells: number of in vivo expanded virus-specific T cells in peripheral blood samples taken at Screening, Day 0, Day 7 to Week 15 after T-cell transfer.

Assessment of the number and viability of CD3+ cells and percentage of IFN-gamma+ cells and cellular composition in the IMP.

Drop-out rate at Day 0 and reasons for drop-out.

Number of days from Screening to Day 0 (day of T-cell transfer).

Documentation of incidence, severity and type of adverse events from Day 0 to Week 8 and serious adverse events throughout the study.
Physical examination and vital signs from Screening to Week 8; Karnofsky/Lansky

index will be assessed at Screening and at Week 8.

Laboratory values for clinical chemistry and haematology from Screening to Week 8.

Documentation of all concomitant medication from Screening to Week 8.

During follow-up Week 15, only antiviral therapy, immunosuppression and SAE-related concomitant medication as well as chemotherapy will be documented.

Non-therapeutic DLI has to be documented as concomitant medication (definition see exclusion criteria).

Treatment with multivirus-specific T cells after Week 8 will also be documented as concomitant medication.

Study description

Background summary

For a growing number of patients suffering from various conditions as, e.g., haematological malignancies or diverse genetic disorders, haematopoietic stem cell transplantation (HSCT) or bone marrow transplantation offer the only possible curative options. However, HSCT is associated with three major risks: graft rejection, graft-versus-host disease (GvHD) and opportunistic, mostly viral, infections or reactivations resulting from delayed immune reconstitution. Delayed immune reconstitution, however, often is the direct result of the severe pre-transplantation conditioning treatment and T-cell depletion of the transplant necessary to fight the risks of graft rejection and GvHD. Therefore, the risk for life-threatening opportunistic, mostly viral, infections is increased in post-transplantation patients. The most common infections after HSCT are Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Adenovirus (AdV).
The standard treatment approach for viral infections/reactivations is chemotherapy which shows limited efficacy and does not restore immunity. Therefore, effective new treatment options are required for this condition. Previous investigations have shown that sufficient T-cell immunity is essential for the control and prevention of viral reactivations and newly occurring

infections after HSCT. The infusion of T-cells is therefore a promising new approach to treat immune-comprised patients. However, infusion with unselected T cells is associated with an increased risk for GvHD due to the high content of alloreactive T cells. A very promising approach to minimize this problem is to remove alloreactive T cells and enrich, isolate and purify virus-specific T cells.
This approach has been studied for nearly two decades and the data published up to date indicate that virus-specific T-cell responses after adoptive T cell transfer protect against virus-related complications post HSCT and restore T-cell immunity, in particular for AdV-, CMV- and EBV-infections. Despite these promising results, virus-specific T-cell transfer is not yet translated into daily clinical practice due to the lack of prospective clinical trials confirming the efficacy of this treatment approach.
The overall goal of this phase III, double-blind placebo-controlled study is to confirm efficacy of multivirus-specific T cells to bring this treatment method in clinical routine. Multivirus-specific T cells generated in this study will be directed against all three most common post-HSCT viral infections: AdV, CMV and EBV. Thus, T-cell immunity will be restored to fight and prevent new viral infections.

Study objective

This study has been transitioned to CTIS with ID 2024-512321-84-00 check the CTIS register for the current data.

Primary objectives:
Evaluation of efficacy of multispecific T-cell transfer in patients with chemo-refractory viral infections after allogeneic stem cell transplantation

Secondary objectives:
- Incidence and severity of newly occurring GvHD
- Incidence and severity of acute toxicity
- Effect on viral load of underlying viral infection
- Clinical response/resolution of symptoms of underlying viral infection
- Overall survival
- Necessity and duration of antiviral chemotherapy
- Incidence of viral infections other than underlying viral infection: evaluation of putative prophylactic effect of treatment
- Days of hospitalization
- Quality of life
- Effect on the patients' T-cell immunity in vivo
- Quality of the IMP and performance of the CliniMACS® Prodigy
- Evaluation of the drop-out rate
- Evaluation of time from inclusion to administration of the IMP
- Overall safety evaluation
- Concomitant medication

Study design

The study will be a double-blind placebo-controlled randomized phase III trial with one interim analysis. The IMP will be generated automatically by the CliniMACS® Prodigy using the CliniMACS Cytokine Capture System (IFN-gamma) after incubation with MACS GMP PepTivator® Peptide Pools of pp65 (CMV), Hexon 5 (AdV) and EBVSelect for enrichment of multivirus-specific T cells in adult and paediatric patients suffering from chemotherapy-refractory CMV, EBV or AdV infections following SCT. Safety will be primarily assessed by determining occurrence and time to acute GvHD grade II, III or IV and aggravation of pre-existing GvHD at Week 8 after T-cell transfer. However, at Week 15, after T-cell Transfer, incidences of GvHD will also be reported.
Efficacy will be primarily assessed by viral clearance for the 1-3 infections under observation that caused inclusion into the study. Secondary endpoints are incidence and severity of acute toxicity, the new occurrence of acute and chronic GvHD, effect on viral load (number of patients reaching >=1 log decrease in viral load), clinical response or resolution of symptoms, overall survival, necessity and duration of antiviral chemotherapy, incidence of CMV, AdV or EBV viral reactivations, days of hospitalization and quality of life. Effects on the patients* immunity will be determined by T-cell phenotyping and analysis of in vivo expanded virus-specific T cells. To assess the feasibility of the T-cell transfer, the drop-out rate and reasons for drop-out as well as the time from patient inclusion to administration of the IMP will be documented. Physical examinations, vital signs and safety laboratory parameters will also be documented until Week 8 of the study. Occurrence of adverse events/serious adverse events and concomitant medication will be monitored and documented in the eCRF as described in protocol section 8.3.

Intervention

Drug Substance
Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of Cytomegalovirus, Adenovirus and Epstein-Barr virus
Drug Product (IMP)
Suspension of multivirus-specific T cells in 20 mL of 0.9% NaCl with 0.5% HSA
Total dose IFN-gamma+ T-cells: 0.1 x 10e4 - 2.0 x 10e7 IFN-gamma+ T-cells
Min. dose T-cells/kg: 10 T-cells/kg recipient bodyweight
Max. dose T-cells/kg:
- HLA-matched (8/8) donors: 1.0 x 10e5 T-cells/kg recipient bodyweight
- HLA-mismatched donors: 2.5 x 10e4 T-cells/kg recipient bodyweight

Study burden and risks

Potential study-specific Benefits for Recipients:

Recovery from therapy-refractory Infection
According to the Investigator*s Brochure (IB) 181 of 246 patients reported up to present (74%) responded to adoptive transfer of virus-specific T cells generated either by in vitro stimulation and expansion, direct isolation via MHC multimers or direct isolation via CCS.

Reduced Rate of new CMV, EBV or AdV Infections/Reactivations
In 7 patients treated prophylactically with CMV-specific T cells produced with CCS so far, no infections occurred within 6 months after treatment. The new approach of using multivirus-specific T cells, which may eliminate CMV, EBV and AdV simultaneously, is expected to also reduce the rate of newly occurring viral infections/reactivations in the high-risk patients included in this study.

Reduced Frequency of Hospitalizations
Data on the frequency of hospitalizations and days in hospital will be collected during the planned clinical trial. It is expected that due to the reduced rate of new CMV/AdV and EBV infections, the frequency of the hospitalizations will decrease. However, as no previous data regarding hospitalizations exist to the best of our knowledge, this assumption remains to be confirmed.

Reduced Medication Intake
The sponsor assumes that along with the reduced number of reactivations of the three viruses, the medication intake will be lowered, especially that of antiviral pharmacotherapy. During the planned clinical trial, data on concomitant medication will be recorded until Week 8 after the adoptive T-cell transfer for all medication administered. After Week 8 until the end of the follow-up period only virus-related, immunosuppressive and SAE-related concomitant medication as well as chemotherapy and cellular treatment will be documented.
Adoptive transfer of multivirus-specific T cells is considered to be a promising approach for treatment and prophylaxis of chemo-refractory viral complications in children and adults post SCT with a favorable risk/benefit ratio.

Potential study-specific Risks for Recipients

Graft-versus-host Disease
Acute GvHD remains a major cause of short-term morbidity in patients after an allogeneic SCT. GvHD was induced in 16 of the 105 previously treated patients. Of these 16 cases, only the severity of 7 was clinically relevant; the other 9 were mild. 3 patients experienced a worsening of existing GvHD. The IMP is not expected to have a clinically relevant effect on the GvHD rate in the treated patients. Safety of the patients is one of the primary endpoints of the planned trial and will be monitored closely.

Potential Sensitization to Murine Proteins

Patients receiving multivirus-specific T cells prepared as described might be at risk of developing allergic reactions due to possible residual amounts of murine antibodies in the cellular product. However, up to date, no such adverse events have been reported following administration of virus-specific T cells from any clinical site.

Potential Toxicity of Iron Dextran
No adverse events related to any CliniMACS reagent have been recorded up to the present since market introduction of the CliniMACS System in 1997.

T-Cell Transfer Toxicity
Symptoms of acute T-cell infusion reactions may occure. In 105 patients treated with adoptive transfer of virus-specific T cells using the CliniMACS Cytokine Capture System (IFN-gamma) no infusion toxicities were reported.

Microbial Contamination of T-cell preparations
Potentially, microorganisms causing infectious diseases might be inadvertently introduced in the apheresis product during processing. In order to prevent contaminations, all precautions to maintain sterility will be taken.

Death
In total, 47 of 105 patients treated with adoptive transfer of virus-specific T cells produced with the CliniMACS Cytokine Capture System (IFN-gamma) died. Death due to the viral disease despite adoptive transfer occurred in 24 of these patients.

Concomitant Therapy Toxicities

Fertility, Teratogenicity and Fetotoxicity
No rationale supports the assumption that T-cell transplantation itself may impact fertility or be teratogen or fetotoxic.
As recommended by the Clinical Trial Facilitation Group (CTFG) for clinical trials with IMPs in accordance with Directive 2001/20/EC, women of child-bearing potential (WOCBP) will only be included in the study after a negative serum pregnancy test. Furthermore, WOCBPs and male patients of reproductive potential must agree to use an allowed contraceptive method.

The possible disadvantages and risks of taking part in the study are that patients will have a number of routine tests performed that could be uncomfortable or slightly painful. Related study procedures will be performed by a qualified study nurse, a doctor or phlebotomy trained health care professional within the hospital.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Adult or paediatric patients (>2 months of age) after HSCT suffering from new or reactivated CMV or EBV or AdV infection, refractory to standard antiviral treatment for two weeks (defined as <=1 log decrease in viral load over two weeks) as confirmed by quantitative blood PCR analysis
2. Original HSCT-donor available with an immune response at least to the virus causing the therapy-refractory infection
3. Written informed consent given (patient or legal representative)

Exclusion criteria

1. Acute GvHD > grade II or extensive chronic GvHD at time of T-cell transfer
2. Treatment with steroids (>1 mg/kg Prednisone equivalent) at Screening
3. Therapeutic donor lymphocyte infusion (DLI) from 4 weeks prior to IMP infusion until 8 weeks post IMP infusion. In case of T-cell depleted HSCT, a prescheduled prophylactic DLI <=3 x 10e5 T cells/kg BW is not considered an exclusion criteria.
4. Organ dysfunction or failure as determined by Karnofsky (age >16 years) or Lansky (age <=16 years) score <=30%
5. Concomitant enrolment in another clinical trial interfering with the endpoints of this study
6. Any medical condition which could compromise participation in the study according to the investigator*s assessment
7. Progression of underlying disease (disease that has led to the indication of HSCT, e.g. leukemia) that will limit the life expectance below the duration of the study
8. Second line or experimental antiviral treatment other than Ganciclovir/Valganciclovir, Foscarnet, Cidofovir and Rituximab from Screening until 8 weeks after IMP infusion
9. Known HIV infection. In case patients do not have a negative HIV test performed within 6 months before enrolment in the study, HIV negativity has to be confirmed by a negative laboratory test.
10. Female patient who is pregnant or breast-feeding, or adult of reproductive potential not willing to use an effective method of birth control from Screening until the last follow-up visit (FU6, visit 8) Note: women of childbearing potential must have a negative serum pregnancy test at study entry
11. Known hypersensitivity to iron dextran
12. Patients unwilling or unable to comply with the protocol or unable to give informed consent.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-03-2020
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO

Date:	01-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	15-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	25-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	23-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	18-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-10-2023
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	CTIS2024-512321-84-00
EudraCT	EUCTR2018-000853-29-NL
CCMO	NL67592.000.19