Adult mesenchymal stromal cells to regenerate the neonatal brain: the PASSIoN trial (Perinatal Arterial Stroke treated with Stromal cells IntraNasally)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON50715

Source
ToetsingOnline

Brief title
Stromal cells and the neonatal brain: PASSIoN-trial

Condition

- Central nervous system vascular disorders
- Neonatal and perinatal conditions

Synonym
Neonatal Stroke; PAIS

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMW TAS subsidie

Intervention

Keyword: Brain, Cell therapy, Neonate, Stroke

Outcome measures

Primary outcome

Primary objective is to determine if MSC treatment in (near-)term infants with PAIS is safe. Safety is defined primarily as the absence of treatment-related serious adverse events (SAEs) according to the Consolidated Standards of Reporting Trials, secondly as the absence of dose-limiting toxicity, defined as death within 24 hours after MSC transplantation or anaphylactic shock related to the MSC administration. At least, all patients will be regularly and intensively assessed, including blood sampling and vital signs, before and 24 hours after treatment, until discharge from our hospital.

Secondary outcome

Our secundary objective is to determine if MSC treatment in (near-)term infants with PAIS is safe at the subacute and 'long-term' setting:

* To determine if MSC treatment in (near-)term infants with PAIS is safe in the subacute setting. Subacute safety is defined primarily as the absence of treatment-related serious adverse events (SAEs) according to the Consolidated Standards of Reporting Trials (chapter 7.2) until the age of 3 months. Patients will then be asked to report on other SAEs, including infections.

* To determine if MSC treatment in (near-)term infants with PAIS is safe at 3

months in terms of cerebral tumorigenicity. To assess safety of MSC treatment on the brain, infants will be scanned using MRI prior to MSC treatment and at 3 months of age. Long-term adverse effects on the brain in terms of tumorigenicity will be determined using this MRI, which is part of regular stroke follow-up program.

Study description

Background summary

Cerebral palsy (CP) is a heterogeneous syndrome with a prevalence between 1.0 and 2.4 per 1000 live births. Perinatal arterial ischemic stroke (PAIS) is one of the most important etiologies for CP and occurs in about 1 per 2300 live births. Unilateral spastic cerebral palsy (USCP), occurring in about 60% of the infants and other common problems including epilepsy, cognitive, speech and behavioral problems. Because of the large and long-lasting burden of the consequences of PAIS for patients and society, development of a treatment strategy for these vulnerable infants is urgently needed. The overall aim of this project is to fill this void by developing an adult mesenchymal stem cell (MSC) based treatment strategy to reduce the life-long consequences of neonatal brain damage. We have already demonstrated in a mouse model of neonatal ischemic infarction that intracerebral application of murine adult bone marrow-derived MSC markedly improves outcome. Treatment with MSC reduced infarct size by >45%, stimulated formation of new neurons and oligodendrocytes, partially restored cortico-spinal motor tract activity, and improved sensorimotor outcome. Moreover, our most recent findings indicate that MSCs can be successfully administered to the brain via an efficient non-invasive route, the nasal route. Upon application to the nasal mucosa, MSCs cross the cribiform plate and migrate into the brain via the rostral migratory route. The MSCs subsequently accumulate predominantly in the infarcted area. The migration of intranasally administered MSCs was also confirmed in experiments with neonatal primates. Notably, in rodent models, MSCs delivered via the nasal route reduce infarct size and improve motor function to the same extent as MSCs administered intracranially/directly into the brain tissue. In the preclinical part of this ZonMw study, experimental research to the efficacy and in particular to the safety of allogenic MSC treatment in the developing species, in which we focussed on inflammatory activity and formation of malignancies in long-term studies, did not reveal any negative/adverse effects concerning these complications in the MSC-treated animals as compared to a non-treated control group. We furthermore found that it was possible to safely manufacture *off the

shelf* MSCs from healthy human donors in our GMP-accredited Cell Therapy Facility (CT-F) of the University Medical Center Utrecht and to culture them for nasal application to term newborns diagnosed with PAIS.

Study objective

This study will assess safety and feasibility of bone marrow-derived allogeneic MSCs, as administered by the nasal route, in neonates who suffered from PAIS. The ultimate goals of the present study is therefore to develop a therapy using adult human allogenic MSCs to reduce or even to prevent the lifelong consequences of perinatal arterial ischemic stroke (PAIS)-related brain damage in this group of term newborns.

Study design

A phase I/II, open-label, single-arm, single-center intervention study in the NICU at the Wilhelmina children*s Hospital / University Medical Centre in Utrecht of (near-)term newborns *36 weeks of gestation within the first week of onset of presenting clinical symptoms. All eligible consecutively admitted patients with a PAIS involving the territory of the middle cerebral artery will be treated with allogenic human MSCs. Since (1) our primary objective is safety and feasibility aspects; (2) the absolute number of PAIS patients will be low, and (3) determination of the infarction volume and brain growth using advanced (volumetric) MRI are already routinely used for a long time, we choose to use this model of investigation. The most important reason to do so is to accomplish the present study in an acceptable inclusion period of 1-2 years. We want to emphasize that the principal reason of the present study is to assess safety and feasibility of MSC treatment in neonates with PAIS. After positive results from this study it will be probable that treatment with human adult MSCs provide us with a substantial better outcome using this relatively stable PAIS model. In the long run this may open the possibility to use MSCs also for the improvement of treatment modalities of other perinatal complications such as perinatal hypoxic-ischemic encephalopathy (birth asphyxia) or prematurity.

Intervention

Based on preclinical data already obtained we anticipate the following ranges for the treatment protocol: the infants will be treated with one dose of 50 million MSCs via the nasal route within within the first week of onset of presenting clinical symptoms. More in detail: prior to MSC administration, a bacterial culture will be taken from both nostrils. Next: 30 minutes prior to delivery of the cells, the nose will be cleaned with saline using standard procedures operative in the NICU. Subsequently we will bring a sterile plastic (e.g. 10cc) syringe alternatevely in both nostrils and drip the MSCs slowly into the nose. The syringe with MSC will be packaged at the CT-F of the UMC Utrecht and will be transported to the participating centers by the clinical

research nurse. Newborns of the other participating centers will be transported to the NICU of the unversity Medical Center Utrecht after MRI confirmation of PAIS to undergo the procedure as described above. Before and 24 hours after MSC treatment, blood samples will be drawn from all infants via in-place arterial/venous catheter.

Study burden and risks

- The extra burden of the present study for the included infants is considered to be very limited -to-non-existent given the fact that besides the nasal treatment to apply the MSCs treatment is not different compared to the acting treatment protocol. Nasal application of MSCs has been considered as non-invasive.
- With respect to possible risks of the present MSC treatment, the most important potential risk factors, inflammatory actions of MSC therapy with allogenic human MSCs and an increased risk for malignancies, are intensively investigated in the preclinical part of the present study. No single indication has been found in experimental research in the developing animal models that above mentioned complications occur in a higher incidence as compared to non-MSC-treated animals, whereas the possibilty for a substantial better short- and long-term outcome seems very realistic on the basis of our previous experimental research data.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

* (Near-)Term infants, *36+0 weeks of gestation, admitted to one of the Dutch NICUs, diagnosed with PAIS, confirmed by MRI within 7 days after presentation with clinical symptoms.
* PAIS as characterized by a predominantly unilateral ischemic lesion within the territory of the MCA, with involvement of the corticospinal tracts, cortex, white matter and basal ganglia.
* Written informed consent from custodial parent(s).

Exclusion criteria

- Any proven or suspected congenital anomaly, chromosomal disorder, metabolic disorder.
- Presence of an infection of the central nervous system.
- No realistic prospect of survival, (e.g. severe brain injury), at the discretion of the attending physician.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-02-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	19-10-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-02-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-08-2020
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-09-2020
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
EudraCT	EUCTR2014-001912-20-NL
Other	https://clinicaltrials.gov/ct2/show/NCT03356821
CCMO	NL59265.000.16

Study results

Date completed:	27-07-2021
Results posted:	03-06-2022

First publication
01-06-2022