An exploratory, open label, multiple dose, multicentre phase I/II trial evaluating safety and efficacy of prenatal and/or postnatal infusion of allogenic expanded fetal mesenchymal stem cells for the treatment of severe Osteogenesis Imperfecta compared with historical and untreated prospective controls.;In the Netherlands patients will not be treated. Retrospective and prospective control patients will be included

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This study has been transitioned to CTIS with ID 2023-504593-38-00 check the CTIS register for the current data. The aim of this trial is to infuse multiple doses of human 1st trimester liver-derived MSC for the treatment of severe OI to determine...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52466

Source
ToetsingOnline

Brief title
BoostB4: Boost Brittle Bones Before Birth

Condition

- Congenital and hereditary disorders NEC

Synonym
Brittle bones disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Swedish Research Council (921-2014-7209),Grant Agreement Number 681045 BoostB4 European Commission

Intervention

Keyword: BoostB4, Fetal therapy, Osteogenesis Imperfecta, Stem cells

Outcome measures

Primary outcome

Primary objectives:

To assess safety and tolerability in the child, fetus and woman after postnatal

or prenatal and postnatal intravenous administration of 4 doses of BOOST cells

every 4 months in subjects with OI type III or severe type IV.

Secondary outcome

Secondary objectives:

To assess the effect of intravenous administration of 4 doses of BOOST cells

every 4 months in subjects with OI type III or severe type IV on:

1. Number of fractures from baseline to primary and long-time follow-up

2. Time (days) to first fracture after last dose

3. Number of fractures at birth (prenatal treatment group only, and postnatal

treatment group when available)

4. Bone mineral density (BMD)

5. Growth

6. Clinical status of OI

7. Biochemical bone turnover

Exploratory objectives

1. To study the impact of 4 doses of fetal MSC on Quality of Life (QoL)

2. To study the extent of donor cell engraftment in tissue samples

3. To study paracrine effects of 4 doses of fetal MSC

4. To study the effect of 4 doses of fetal MSC on endogenous immune cells

5. To study non-invasive prenatal diagnosis of OI (will not be used in the

diagnostic procedure in the trial)

Study description

Background summary

Osteogenesis Imperfecta (OI), or brittle bone disease, is a debilitating congenital disorder with prenatal onset leading to osteopenia and bone brittleness. Affected children and adults suffer from repeat, multiple bone fractures, requiring hospitalisation and surgery, often leading to irreversible deformities in severely affected individuals. Diagnosis is usually made at the routine fetal anomaly ultrasound scan performed mid-pregnancy in countries in the European Union (EU) during pregnancy, where the characteristic shortened long bones and fractures are already present and detectable.

OI is a group of genetic disorders caused mainly by >1,400 different dominant and >150 recessive mutations. One child among 10-20,000 is born with OI and mutations in the collagen genes resulting in abnormal collagen microfibril assembly are most common in the moderate/severe types. The major clinical manifestations are atypical skeletal development, osteopenia, multiple painful

fractures and short stature, but >50% of OI individuals also suffer from brittle teeth, hearing loss and hypermobile joints and there is also a higher risk of heart valve insufficiency, aneurysms and bleeding and coagulation deficiencies throughout their lifetime. OI presents in a clinically heterogeneous manner, ranging from the mild type I that may only become evident in adulthood to the perinatally lethal type IIA/C. Life expectancy is not affected in milder OI types but may be shortened for those with more severe types. Type III OI is the most severe form that is compatible with survival into adulthood. Individuals affected by OI type III may experience hundreds of fractures in a lifetime. Type III is the most severe forms in children surviving the neonatal period, manifesting with extremely short stature and multiple painful fractures, spinal deformities and kyphoscoliosis predisposing to premature respiratory death in the most severely affected cases. However, most commonly OI presents in childhood with multiple fractures after little or no trauma (type I/mild type IV). OI type IV results in reduced stature and is moderately deforming.

Whole-body dual energy X-ray absorptiometry (DXA) images of adults with OI shows the wide spectrum of skeletal manifestations in OI; from the mild abnormalities in type I OI to the severe deformities in type III OI. The arrowheads indicate orthopaedic rods in the long bones and the arrows indicate fragmentation of the epiphyseal growth plates (*popcorn epiphyses*). One individual with type IV OI underwent amputation of both legs owing to multiple fractures.

There is no cure for OI, with the only current pharmaceutical treatments being symptomatic and inadequate in reducing long bone fracture frequency and failing in addressing the underlying molecular pathology, the bone brittleness and collagen defect. Treatment is aimed at increasing overall bone strength to prevent fractures and maintain and/or increase mobility. This is accomplished with physical therapy to strengthen the muscles and improve mobility and life-long orthopaedic interventions such as the insertion of rods in the long bones to correct bone deformities. Bisphosphonates (BP) are used to reduce bone resorption and increase bone mass. However, two recent meta-analyses of randomised trials on BP treatment for OI did not demonstrate improvement in fracture rates, reduction of pain or functional mobility.There is also growing concern regarding the role of BP in causing impaired bone remodelling in these children, which may be counterproductive. A study has demonstrated that individuals with OI are in need of most care at age 1-14 years with a high demand on hospital services [12], which shows the importance of taking action early against this destructive disease. Thus, new treatment modalities are needed. Infusion of stem cells that produce healthy collagen and that can engraft into damaged bones and support the development of new normal bone is an approach that holds great promise for OI individuals, and as described below, prenatal treatment may be even more efficacious than postnatal treatment.

Across Europe, prenatal diagnosis of severe OI is commonly suspected at the

routine anomaly scan conducted around 18-20 weeks of gestation. A prenatal diagnosis of OI cannot be confirmed without a molecular diagnosis from fetal genetic material obtained following amniocentesis or chorionic villus sampling. The result is often not available before 21-22 weeks of gestation, which is a common deadline for termination of pregnancy in some countries. Couples, even if they might consider termination of pregnancy as an option, may not therefore be offered the choice. Prenatal therapy using fetal mesenchymal stem cell (MSC) infusion gives couples a third option, to treat the fetus before birth. In addition, a significant proportion of parents do not want to terminate a pregnancy, but want to improve the situation of their child irrespective of the severity of the fetal disease detected. Such couples could soon be offered prenatal therapies. Finally, prenatal treatment may have clinical advantages over postnatal approaches (see section 4.3 of the protocol).

Study objective

This study has been transitioned to CTIS with ID 2023-504593-38-00 check the CTIS register for the current data.

The aim of this trial is to infuse multiple doses of human 1st trimester liver-derived MSC for the treatment of severe OI to determine the safety, tolerability and clinical effectiveness of prenatal and/or postnatal infusion of same-donor fetal MSC. The trial will provide data to support the future clinical development and commercialisation of this therapy. We will also assess the potential of non-invasive methods of prenatal diagnosis for OI for improved clinical translation of prenatal therapeutic approaches. The trial will be conducted in compliance with the Clinical Trial Protocol, Good Clinical Practice (GCP), the Declaration of Helsinki and the applicable regulatory requirement(s).

Severe OI is an incapacitating inherited chronic disease with no curative or sufficiently effective treatment. OI causes damage already in fetal life. Therefore, it is desirable to introduce treatment as early as possible before additional pathology occurs and at a time of rapid skeletal development. MSC may ameliorate OI, and can be administered before and/or after birth, suggesting a potential treatment of OI. Persons with severe types of OI are seriously ill and suffer from multiple disabilities and chronic pain through their lifetime. A prenatal or early treatment of this severe disorder would therefore be of benefit. Even though a single prenatal infusion may not be clinically sufficient for permanent improvement, a prenatal infusion approach is still justifiable since the immunological naïveté of the fetus may allow for the development of immune tolerance towards the donor cells rendering postnatal booster infusion more efficient. Pre-clinical studies show that early treatment either in utero or in neonatal mice is more effective at treating OI than later treatment [38, 39]. In addition, as the infusion is given into the umbilical vein in the fetus, it will bypass the pulmonary circulation via two fetal shunts, the ductus venosus and the foramen ovale. This ensures that the infused

MSC go directly into the systemic circulation and can then home directly to the bones. MSC infusion after birth is performed into a peripheral vein, with many MSC becoming trapped in the microcirculation of the lungs [40-44], before fewer MSC reach the systemic circulation.

The rationale for repeated infusions (four infusions per child) of same-donor MSC postnatally is based on the clinical data from the published studies on stem cell transplantation in OI, where the effect diminished after 3-6 months after transplantation [17, 45, 46], and on our own experience and data [18, 19]. If the child*s developing bones repeatedly are strengthened early in life there is a good chance that the OI phenotype will be less severe also later in life.

The dose of fetal MSC for prenatal and postnatal infusion is approximately 3x106 cells/kg bodyweight. The doses refer to the total number of live cells in the preparation after thawing. The dose is based on our available data on safety and efficacy from pre- and postnatal infusion in fetuses, infants and children [17-19] and our unpublished data on experimental treatment of OI, Gaucher Disease type 2 and bronchopulmonary dysplasia (see the Investigators Brochure, IB).

First trimester liver has been selected as the starting material for the IMP. This is because of the superior characteristic of these isolated cells in comparison to other cell sources. MSC derived from fetal tissues are found at a higher frequency with greater colony-forming capacity, have longer telomeres and a superior proliferative and differentiative capacity [30, 31, 33, 47]. Fetal MSC are also more osteogenic compared to MSC from adult sources [32, 34, 48]. Fetal MSC have, similar to adult MSC, a low immunogenic profile [26, 29]. Lastly, in prenatal transplantation it has been demonstrated that it is better to use fetal than adult cells. Fetal liver cells had a 10 times higher competitive engraftment advantage compared to adult bone marrow cells, and fetal liver cells repopulated 8.2 times better than adult bone marrow cells after prenatal transplantation [49].

Successful clinical demonstration of BOOSTB4 therapy with fetal MSC in OI will pave the way for the treatment of many developmental fetal disorders. Decreasing the severity of these congenital diseases results in life-long benefits for the affected individual from birth onwards, thus providing many decades of quality-adjusted life years. For the parents, providing treatment as soon as a prenatal diagnosis is made rather than waiting until after birth may allay some of the anxiety associated with the diagnosis. It can be concluded that the overall risks (mainly tumour formation, which is calculated to be low and risks associated with the infusion procedure, which is 0.1-1%) posed to the subjects in this trial are low and do not outweigh the potential benefits (see section 16.3 for more information).

In the Netherlands only the historical and prospective controls with OI type

III or severe type IV will be included

Study design

The trial is an exploratory, open label, multiple dose multicentre phase I/II trial of allogeneic human fetal MSC infusion for the treatment of OI type III or severe type IV compared with historical and untreated prospective controls.The trial is divided into a 2-year treatment period (period 1) followed by a non-interventional follow-up period until 10 years after inclusion (period 2). Subjects can be enrolled during the initial 3 years of the treatment period. The maximum treatment time for each subject is 20 months.

Two groups of 30 subjects in total will be enrolled in the trial and these groups will be compared with a third historical and/or prospective untreated control group. The subjects are included in the two groups based on availability and subject to practical issues:
1. Prenatal group: pregnant women whose fetus has been diagnosed with OI type III or severe OI type IV prenatally on ultrasound findings, and confirmed using molecular analysis of fetal genetic material as having a pathogenic collagen mutation
2. Postnatal group: infants diagnosed with OI type III or severe OI type IV on clinical findings, and confirmed using molecular analysis of fetal genetic material as having a pathogenic collagen mutation
3. At least 30 historical and prospective controls with OI type III or severe OI type IV on clinical findings, and confirmed using molecular analysis of fetal genetic material as having a pathogenic collagen mutation

Persons with OI will be recruited from across Europe from three clinical sites in Sweden, the United Kingdom and the Netherlands. Subjects in the prenatal group will be included in the trial before birth between 16 and 35+6 weeks of gestation and subjects in the postnatal group can be included in the trial at three set time points after birth (4, 8 and 12 months of age), and receive treatment at the time points 0, 4, 8, 12 months after inclusion. All time points are defined as ± 1 month.

Subjects in the prenatal group will receive the first treatment prenatally (between gestation weeks 16 and 35+6) and will then be treated and evaluated at 4, 8, 12 months of age and follow-up will be performed 6 and 12 months after the last infusion. Subjects in the postnatal group will be included and receive the first treatment at 4, 8 or 12 months of age (option 1, 2 or 3) and then be treated and evaluated at 4, 8, 12 months after inclusion and follow-up will be performed 6 and 12 months after the last infusion (period 1) All infusions are performed with same-donor cells for each subject. After the follow-up 12 months after the last infusion, all subjects (all children and the mothers where infusion was performed during pregnancy) will be followed for at least 10 years after inclusion in the study (period 2).

Women whose fetus underwent infusion of MSC prenatally will be followed with maternal blood sampling up to 4 months after the birth of their child to analyse for transfer of donor cells and development of donor specific antibodies. After this point, no blood samples will be taken unless clinically indicated. Women taking part in the current trial will be informed that they should notify the BOOSTB4 trial centre and their general practitioner in the event of a future pregnancy.

In short: This will be a multi-centre, open label, multiple-dose, phase I/II trial of allogeneic human fetal MSC infusion for the treatment of OI type III or severe type IV compared with historical and untreated prospective controls.

Intervention

No intervention for Dutch historical and prospective controls.

Study burden and risks

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

INCLUSION CRITERIA

Control group:
a) Matched historical controls
1. Parent*s/legal guardian*s signed informed-consent form
2. Clinical and molecular diagnosis of OI (Glycine substitution in the collagen triple-helix encoding region of either the COL1A1 or COL1A2 gene)
3. Data on fractures and growth is available
4. Parent/legal guardian over 18 years of age

b) Prospective untreated controls
Postnatal participation: The inclusion criteria for the postnatal group apply
Prenatal participation: The inclusion criteria for the prenatal group apply, except inclusion criteria 2.

Exclusion criteria

EXCLUSION CRITERIA

Control group:
a) Matched historical controls
1. Existence of other disorder that might interfere with the trial
2. Abnormal karyotype
b) Prospective untreated controls
Postnatal participation: The exclusion criteria, except exclusion criterium 4, 5, 6 and 7 (Contraindication for invasive procedure, Known risk factor for clotting, Positive Donor Specific Antibody-test and Known allergy/hypersensitivity to Fungizone and/or Gensumycin), for the postnatal group apply.
Prenatal participation: The exclusion criteria, except exclusion criterium 1, 4, 5, 6 and 7 (Multiple pregnancy, Contraindication for invasive procedure, Known risk factor for clotting, Positive Donor Specific Antibody-test and Known allergy/hypersensitivity to Fungizone and/or Gensumycin), for the prenatal

group apply.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-10-2022
Enrollment:	0
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO

Date:	26-02-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	01-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2022
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	CTIS2023-504593-38-00
EudraCT	EUCTR2015-003699-60-NL
ClinicalTrials.gov	NCT03706482
CCMO	NL64015.000.17