The CONCERT study CONgenital Cmv: Efficacy of antiviral treatment in a Randomized controlled Trial

Published: 17-04-2012
Last updated: 26-04-2024

Primary Objective: Investigate whether early valganciclovir treatment of children with SNHL of >= 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent deterioration of the hearing loss at 1 year follow-up.Secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON39229

Source
ToetsingOnline

Brief title
The Leiden CONCERT study

Condition

- Skin and subcutaneous tissue disorders NEC
- Hearing disorders
- Developmental disorders NEC

Synonym
congenital cytomegalovirus (CMV)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Fonds NutsOhra

Intervention

Keyword: cytomegalovirus, sensorineural hearing loss, valganciclovir

Outcome measures

Primary outcome

The primary endpoint is the status of the sensorineural hearing loss expressed in dB, in children with congenital CMV at 1 year follow-up.

Secondary outcome

Secondary endpoints are development (cognitive and motor) at baseline and 1 year follow-up. Communicative and speech development will be assessed at 1 year follow-up. Furthermore, for the treatment group the viral load in blood and urine will be determined at baseline and thereafter weekly during the 6 weeks of treatment and at 1 week after completion of treatment. For the non-treatment group blood viral load will be determined at two time points (t=0 and 6 weeks), and urine viral load will be determined weekly during the 7 weeks after inclusion. At 1 year follow-up the urine viral load will be determined for all included children.

Study description

Background summary

Congenital CMV is a common infection leading to a wide range of clinical signs and symptoms. These include intrauterine growth retardation, microcephaly, cerebral involvement with developmental delay, sensorineural hearing loss

(SNHL) and opthalmological disorders. Transient problems include hepatic damage and haematological disorders (leucopenia and thrombocytopenia). One of the most apparent, frequent and serious consequences of a congenital CMV infection is SNHL. Most children with congenital CMV infection have no symptoms at birth. Of these 85-90 % asymptomatic children, 13.5 % will eventually develop symptoms, such as SNHL but possibly also mental retardation and visual defects.
Due to the wide variety in presenting symptoms caused by a congenital CMV infection, a distinction is made between symptomatic and asymptomatic congenital CMV. Symptomatic CMV infection is defined as a clinically apparent disease in the newborn period including microcephaly, intracranial calcifications, chorioretinitis and abnormal cerebrospinal fluid. Asymptomatic congenital CMV infection includes all children with no clinically apparent disease at birth, also including children with SNHL. This distinction has traditionally existed in literature because hearing impairment was usually not diagnosed until the child was much older.

CMV is the most common cause of congenital infections worldwide. To determine the birth-prevalence of congenital CMV in the Netherlands, a random sample of 6500 dried blood spots (DBS), obtained in 2007 from neonates from all regional screening areas, was tested for CMV. Results show a birth-prevalence of 0.54% (95% CI 0.3-0.7%). This means that every year about 1000 neonates are born in The Netherlands with a congenital CMV infection. Of all children with congenital CMV infection 17-20% will have long-term permanent sequelae. Of those children, 2/3 will be asymptomatic at birth and 1/3 will be symptomatic. These permanent sequelae result in disabilities such as SNHL, visual impairment and mental retardation.
Moderate to severe SNHL affects about one per 1000 newborns in the Netherlands. Early detection of severe hearing loss and subsequent intervention before the age of 6 months has been shown to improve cognitive, social and learning abilities. This is the reason for the recent implementation of universal neonatal hearing screening in the Netherlands. Congenital CMV infection is an important cause of both early and late-onset SNHL, causing 20-30 % of cases. Korver et al recently showed that the rate of congenital CMV among Dutch children with permanent bilateral hearing impairment was 8%, and 23% among children with profound hearing impairment. Only early-onset cases of SNHL will be detected by the neonatal hearing screening.
Several studies have shown the beneficial effect of intravenous ganciclovir and/or oral valganciclovir of hearing preservation in newborns identified with congenital CMV. However, these studies concentrated on infants with symptomatic congenital CMV infections and treated with intravenous ganciclovir. The mentioned studies show a substantial effect of treatment. However, there is not sufficient data available on the treatment of congenital CMV infections whether being symptomatic or asymptomatic, or with the use of oral valganciclovir. Oral treatment should be explored for the obvious reasons of it being less invasive for the patient and without the necessity for hospital admission during the treatment.
An effective and easy to administer treatment for congenital CMV infections may

prevent further deterioration of already existing SNHL and also prevent the development of SNHL in a group where this is not yet apparent and thus cannot be detected by neonatal hearing screening. It is to be expected that other manifestations of congenital CMV infection, such as psychomotor developmental delay might also benefit from early treatment. The diagnosis of congenital CMV infection can be carried out using dried blood spots.
We hypothesize that this study will show that early detection of congenital CMV infection in children with hearing impairment and treatment of infected children, will prevent (deterioration of) hearing loss in a considerable number of children.

Study objective

Primary Objective:
Investigate whether early valganciclovir treatment of children with SNHL of >= 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent deterioration of the hearing loss at 1 year follow-up.

Secondary Objective(s):
Investigate whether early valganciclovir treatment of children with SNHL of >= 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection can prevent cognitive and motor retardation. Communicative and speech development will be extensively assessed. Investigate whether early valganciclovir treatment of children with SNHL of >= 20 dB, unilateral or bilateral, and a confirmed congenital CMV infection reduces the CMV viral load in urine and blood samples 6 weeks treatment and one week and one year after completion of treatment. At 1 year follow-up solely the urine sample will be investigated for the viral load.

Study design

The design of the trial is a randomized controlled trial. Before inclusion of infants, the neonatal hearing screening program is fulfilled. All children in the Netherlands are screened for hearing loss. First with Otoacoustic Emissions (OAE). When this test is not passed with both ears, a second OAE is carried out. In case the second OAE is not passed with both ears the Auditory Brainstem Response (AABR) is conducted. An infant is referred to an Audiological Center (AC) when the AABR is not passed for both ears. Specific for the trial, parents of all infants referred to an AC will be asked for informed consent to test the heel stick card (previously routinely obtained for metabolic screening in the first week of life) for congenital CMV. The parents of the children whose test is positive for a congenital CMV infection and who are diagnosed with hearing loss (>=20dB) at an AC will be asked for informed consent for participation in the RCT. After consent has been given, a home visit is planned with parents for inclusion of their child in the RCT. The child is randomized to the treatment or the non-treatment group. The day after inclusion treatment is started for 6

weeks in the treatment group. Children in the non-treatment group receive no additional medication. Besides the extra care for the children in the trial, all standard care continues (hearing aids, extra hearing evaluations and all other standard care procedures necessary). At 1 year follow-up hearing and child development are assessed. Hearing will be assessed at an AC, child development will be assessed during a home visit and parents will fill in a questionnaire concerning the development of their child. The hearing assessment and child development testing at 1 year follow-up constitute extra investigations on top of the standard care program. A few infants will have a second hearing evaluation requested by the AC as standard care. When this hearing evaluation is within 1 month prior or post the moment of 1 year follow-up, no additional hearing evaluation will be necessary for the trial at 1 year follow-up.

Target population
In the last three years, an average of 580 infants per year were referred to an AC. According to the literature we can expect 25% of congenital CMV infected infants with SNHL to develop hearing loss at a later stage (late-onset hearing loss), up to several years of age. This implies that these infants will pass the neonatal hearing screening. When calculating the target population for this RCT we have taken into account that 8% of infants with bilateral hearing loss will have a congenital CMV infection. For the infants with unilateral hearing loss approximately 20% will have a congenital CMV infection. Taking the late-onset hearing loss into account, 6% of infants with bilateral hearing loss will present in de neonatal hearing screening with hearing loss. For the infants with unilateral hearing loss, 15% will present in the neonatal hearing screening with hearing loss. The above numbers have been calculated according to extensive literature review. A proportion of infants referred to an AC will appear to have normal hearing after audiometry (hearing loss < 40 dB). In the Netherlands the threshold for hearing loss is defined as >= 40 dB in the best hearing ear. For the trial hearing loss is defined as >= 20 dB in one or both ears. As a result, a few children diagnosed with normal hearing in the screening program do belong to the target population of the trial. It is unclear as of yet how many infants this will be. These infants cannot be included in the trial as these children may never or later be diagnosed with hearing loss.
For the years 2008 and 2009 all data has been received and summarized in a final report. Because the results of the neonatal hearing screening program of the years 2008 and 2009 are the only ones fully available, these will be used in the following calculation for the target population.
In the years 2008 and 2009, 96 and 82 infants respectively were diagnosed with unilateral hearing loss. With the 15% mentioned above when taking the late-onset cases of hearing loss into account, it can be concluded that 12-15 infants will suffer from a congenital CMV infection. In 2008 and 2009, 136 and 163 infants respectively were diagnosed with bilateral hearing loss. Taking the above mentioned 6%, 8-10 infants will suffer from a congenital CMV infection. Concluding, a total of 20-25 infants referred after neonatal hearing screening

can be expected to suffer from a congenital CMV infection on a yearly basis. Considering that for the trial hearing loss of >20dB makes the neonate eligible for inclusion makes the number of infants suitable for inclusion higher. Quantification of how many infants this would be is as of yet not possible due to a lack of sufficient data concerning this specific group of infants with hearing loss of 20 - 40dB.

Intervention

Treatment group: Oral valganciclovir 32 mg/kg per day in two doses during 6 weeks.
Non-treatment group: no medical intervention besides standard care.

Study burden and risks

One of the main benefits of this trial is the chance of preventing deterioration of hearing loss for the children treated with valganciclovir. The benefit for the untreated as well as for the treated children diagnosed with congenital CMV will be extensive follow-up with laboratory tests, extra physical examinations, extra developmental tests and extra hearing evaluation. Besides the above mentioned benefits, another benefit associated with participation is the possibility of early recognition of a cause of SNHL in children in whom otherwise the cause of the SNHL will most often remain unknown. This will provide information on prognosis and chances of other children in the family suffering from hearing impairment of having a congenital CMV infection.

At follow-up all children will be physically examined, audiometric examination will be carried out and the cognitive and motor development will be investigated. Early habilitation
of hearing loss is known to have a significant impact on the communicative, emotional, cognitive, social development and quality of life (18). Besides correction for the hearing loss, other adjustments (such as learning sign language and special education) will benefit the infant.
The most important possible disadvantages for participation are potential side effects of valganciclovir, most importantly reversible neutropenia. In the treatment group the potential side effects are carefully monitored by means of weekly blood tests during the treatment period of six weeks, (See dosage modifications 3.6). The blood samples will be taken by a study group member at the home of the infants.
During the 1 year follow-up, the following examinations will be carried out: history taking, physical examination, parental questionnaire, blood tests (treatment group: 0-6 weeks during treatment, 1 week after completion of treatment and 1 year follow-up; non-treatment group: two blood samples at inclusion and 6 weeks post inclusion), urine tests with filter paper in the diaper (weekly during 7 weeks after inclusion and at 1 year follow-up), hearing

tests at an AC (baseline and 1 year follow-up) and developmental scores at the home and a developmental questionnaire (1 year follow-up).

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Infants with congenital CMV infection, and hearing loss (>= 20 dB, in one or both ears).
- Age at time of inclusion is <= 12 weeks after birth.
- >= 37 weeks gestational age.
- Birth weight >= 2500 gram.
- Parental signed informed consent.

Exclusion criteria

- Indications for symptomatic congenital CMV infection based on diagnostics carried out prior to the inclusion of the child in the trial.
- In case during the house visit the presence of a symptomatic CMV infection is doubted, inclusion will be discussed. Depending on the medical history taking, physical examination and laboratory tests inclusion will be decided upon.
- Treatment with other antiviral agents or immunoglobulins.
- Leucopenia < 0,5 x 10*9/L (blood sample tested at t=0).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-09-2012
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Valcyte
Generic name:	Valganciclovir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-04-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-05-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-06-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-07-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-04-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-04-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2011-005378-44-NL
CCMO	NL36483.058.12