Is early revaccination after ALL therapy feasible ?
Evaluation of loss of antibodies and responsiveness to (re-)vaccination in children after treatment for acute lymphocytic leukemia.

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To determine effect of early (re) vaccinations after the current intensive chemotherapy for ALL. We will determine if there is a difference in respons to conjugated (T cell dependent) and polysaccharide (T cell independent) vaccines. This may result...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON33573

Source
ToetsingOnline

Brief title
EVA study

Condition

- Leukaemias

Synonym
acute lymphocytic leukemia, leukemia

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: foundation for children with cancer (stichting kika)

Intervention

Keyword: Acute lymfocytic leukemia, children, secundary immunodeficiency, vaccination

Outcome measures

Primary outcome

Effect of revaccinations early after end of chemotherapy

Data will be reported in terms of proportions of patients who experienced seroconversion (defined as a >= 4- fold increase in antibody concentration or titer) and who attained protective concentrations or titers. Using a responder analysis these patients will be defined as responders.

Effect of vaccination with polysaccharide pneumococcal (T cell indepedent) en conjugate pneumococcal vaccination (Tcel dependent)

Secondary outcome

How is the immunophenotyperic reconstitution as measured in blood correlated to immunoglobulin levels and specific antibody titers before and after vaccination.

Study description

Background summary

Tailored and intensified therapy for children with ALL (acute lymphatic leukaemia) has led to an improved 5 years survival, instead of the earlier 80%,

it approaches now the 90%. (1-5) Attending this low mortality rate after the end of treatment means preventing invasive vaccin preventable infections. There are only a few studies with respect to the incedence of such diseases. (11-14) Chemotherapy is immunosuppressive, it causes a decrease of the number of B and T cells. The immunity against infections is diminished, there is a loss of protective antibody level provided by previous immunizations and reduced efficacy of (re-) immunization. (16,17)
It is still not clear if and when children require revaccination after completion of chemotherapy for ALL. The numbers of B and T-cells increase from 3 months after the end of treatment but a complete recovery may take up to 1 year. (11-13) The number of B cells is recovering faster than the CD4 T helper cells. (13,14) The number of memory T cells remain mostly intact. Quick (re-) vaccination, keeps the vulnerable period for potentially very threatening diseases as short as possible. A recent survey showed a good response on (re) vaccination (H. influenzae B, Tetanus, Meningokokken C, Polio and Measles) 6 months after the end of chemotherapy. (25) This response may differ for conjugated (T cell dependent) and polysaccharides (T cell independent) vaccines, this hasn't been investigated in this population. We've included both types of pneumococcal vaccine in the (re) vaccination program. The use of both vaccins will result in the expansion of serotype coverage in the high risk children and older age groups. Besides we know children with ALL carry a more than 10-fold higher risk of invasive pneumococcal disease than the general pediatric population. (11,12)

Study objective

To determine effect of early (re) vaccinations after the current intensive chemotherapy for ALL. We will determine if there is a difference in respons to conjugated (T cell dependent) and polysaccharide (T cell independent) vaccines. This may result in a guideline for the revaccination of children treated with standard antileukemia chemotherapy in the Netherlands.

Study design

Prospective multicenter study.
Patients will be revaccinated with the DKTP-Hib, BMR, MenC and 7 valent conjugate pneumococcal vaccines from the Dutch National Infant Vaccination Programme and will be vaccinated with 23- valent polysaccharide pneumococcal vaccine, after they finished DCOG ALL10 protocol treatment. Responses will be measured in serum 4 weeks after each vaccination. Simultaneously, immunophenotypic reconstitution will be measured by flowcytometry.

Intervention

Prospective multicenter trial. The study will take place in 4 university medical centers in the Netherlands. (UMC Utrecht, VU MC, AMC and UMCG) .The

duration will be 7 months. In the flow chart below an overview of the procedures that subjects will undergo in the course of research.

T= -1 month
- To fill in a questionnaire (part of the CRF); questions about their pre- ALL vaccination status, if they had immunoglobulins during treatment etc.

T=0 months (after completion chemotherapy = END ALL10 chemotherapy, ± 2 weeks)
- Venapunction (VP) 1 (during anesthesia for regular ALL 10 treatment bone marrow
puncture)
- Immunophenotyping (UMC Utrecht only)
- Serostatus DKTP-Hib, BMR, MenC, Pneu
• If the patient has a protective serostatus* against each vaccine preventable disease he/she will be excluded from the rest of the study.
• If the patient has a protective serostatus* against >= 1 of each vaccine preventable he/she will not be vaccinated against these diseases, but will get the vaccines against the diseases he/she is not protected to..

T=3 months (± 2 weeks)
- VP 2
- Serostatus DKTP-Hib, BMR, MenC, Pneu
- Immunophenotyping (UMC Utrecht only)
- Vaccination in separate limbs:
- DKTP-HiB vaccine (Pediacell+Hib®): 0,5 ml i.m.
- 7-Valent Pneumococcen conjugaat vaccine (Prevenar®): 0,5 ml i.m.

T=4 months (± 2 weeks)
- VP 3
- Serostatus DKTP-Hib, BMR, MenC, Pneu
- Vaccination
- 7-Valent Pneumococcen conjugaat vaccine (Prevenar®): 0,5ml i.m.
- Meningococcus type C conjugaat vaccin (NeisVac-C®): 0,5 ml i.m.

T=5 months (± 2 weeks)
- VP 4
- Serostatus DKTP-Hib, BMR, MenC, Pneu

T= 6 months (± 2 weeks)
- VP 5
- Serostatus DKTP-Hib, BMR, MenC, Pneu
- Immunophenotyping (UMC Utrecht only)
- Vaccination in separate limbs:
- Pneumococcal vaccine 23-valent polysaccharide (Pneumo 23®): 0,5 ml i.m
- BMR-Vaccine RIVM: 0,5 ml s.c. (upper arm)

T= 7 months (± 2 weeks)
- VP 6
- Serostatus DKTP-Hib, BMR, MenC, Pneu

* Protected when:
- DKTP-HiB vaccine: Hib, anti-PRP antibody concentrations >=1, 0 µg/mL
- 7-Valent Pneumococcen conjugaat vaccine: a geometric mean concentration of >= 0, 35
µg/ml.
- Pneumococcal vaccine 23-valent polysaccharide: a geometric mean concentration of
>= 0, 35 µg/ml.
- Meningococcus type C conjugaat vaccine SBA titer >=1:128.
- BMR-Vaccine: Any detectable titer of neutralizing antibody against poliovirus. For measles,
a concentration>= 120 mIU/mL.

Study burden and risks

Burden:
6 venapunctures
a maximum of 5 i.m. injections
a maximum of 1 s.c. injection

Risk:
Vaccination reaction

Benefit:
Protection against vaccine preventable diseases

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)

Inclusion criteria

Patients who finished DCOG ALL-10 (Medium Risk) protocol treatment.
age between 3 - 21 years old (inclusion criteria for ALL10 protocol is 1 year till 19 years old, treatment takes 2 years)

Exclusion criteria

History of allergic response to vaccination
Patients with Down syndrome
Patients with acute leukaemia classified as standard and high risk according to the Dutch DCOG ALL-10 protocol.
Patients with a stem cell transplantation in history
Objection to vaccination because of religious reasons
Patients with a congenital immunodeficiency

Study design

Design

Study phase:	3
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2009
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	MMR vaccine
Generic name:	mumps, measles rubella vaccin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NeisVac-C
Generic name:	Meningococcal vaccin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pediacel
Generic name:	Pediacel diphtheria, tetanus, five component acellular pertussis, inactivated poliomyelitis and Haem
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pneumo 23
Generic name:	Pneumo 23, 23 valent polysaccharide pneumococcal vaccine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prevenar
Generic name:	Prevenar, pneumococcal conjugate vaccine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-07-2009
Application type:	First submission
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	EUCTR2008-008278-29-NL
CCMO	NL16858.000.09