Study of expression of and immunity against neoantigens in patients with constitutional mismatch repair deficiency (CMMR-D) syndrome

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In this explorative study, we aim to:• Analyze neoantigens expressed on different tumors of CMMR-D patients, to identify possible target antigens for DC vaccination studies.• Investigate the presence of pre-existing immune responses against...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON49277

Source
ToetsingOnline

Brief title
Immunity against neoantigens in CMMR-D

Condition

- Congenital and hereditary disorders NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
bi-allelic Lynch syndrome, Biallelic MisMatch Repair Deficiency (BMMRD)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: KiKa

Intervention

Keyword: CMMR-D, immunity, neoantigens

Outcome measures

Primary outcome

The primary endpoints of the study are the identification of neoantigens on

different tumors of CMMR-D patients and the detection of pre-existing immune

responses against neoantigens

Secondary outcome

n.a.

Study description

Background summary

CMMRD
In 1999, a recessive paediatric tumor predisposition syndrome called Constitutional Mismatch Repair Deficiency (CMMR-D) syndrome was recognized. CMMR-D syndrome is caused by homozygous or compound heterozygous germline mutations in one of the DNA mismatch repair (MMR) genes. Mainly three types of malignancy characterize this syndrome: gastrointestinal tract cancer, haematological malignancies and brain tumors, which occur in childhood or adolescence. If patients survive the first malignancy, they have a high chance of developing a second or even a third malignancy. To date, patients with CMMR-D are intensively screened but this does not guarantee the detection of precancerous lesions or cancer at a curable stage. A preventive treatment modality would therefore be a major step forward.
Due to germline mutations in MMR genes coding for proteins involved in repair of nucleotide mismatches, truncated proteins with impaired function are formed. These aberrant proteins can be recognized by the immune system and they might

be excellent targets for immunotherapy since only tumor cells express them.

DC vaccination
Dendritic cells (DCs) play a central role in the induction of immune responses. During an infection, DCs become activated and migrate to the lymph nodes where they stimulate specific killer T cells. Their decisive role in inducing immunity formed the rationale for DC immunotherapy: DCs loaded with tumor antigens are injected into cancer patients to stimulate T cells to eradicate tumors. In experimental clinical studies, DC vaccination has led to effective anti-tumor immune responses and increased survival in patients with melanoma. In healthy Lynch syndrome carriers, who have only a mono-allelic mutation in their DNA mismatch repair system, DC vaccination has led to induction of neoantigen-specific T cells, without inducing serious side effects.

DC vaccination of CMMRD
In this study we want to develop a preventive treatment for children with CMMRD. We aim to induce immune responses against neoantigens with DC vaccines, to prevent the formation of new lesions. For this, we need more knowledge of the presence of neoantigens and immune responses in tumors of CMMRD patients. In this explorative study, we will make an inventory of neoantigens expressed by different tumors of patients with CMMRD syndrome, to select/identify possible target antigens for DC vaccination studies. In addition, we will investigate the presence and specificity of pre-existing immune responses against neoantigens in blood of CMMR-D patients. The results of this study will be translated into the development of a preventive DC vaccine for children with CMMRD in a follow-up study.

Study objective

In this explorative study, we aim to:
• Analyze neoantigens expressed on different tumors of CMMR-D patients, to identify possible target antigens for DC vaccination studies.
• Investigate the presence of pre-existing immune responses against neoantigens in CMMR-D carriers.

Study design

This study is a single arm exploratory, multi-centre study

Study burden and risks

There are no additional risks to participation in this study other than that of regular blood collection. The burden for the participants is minimal, as blood collection for the study will take place during regular blood collection.

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 with genetically proven Constitutional Mismatch Repair Deficiency (CMMRD)
• Signed informed consent

Exclusion criteria

• Any form of comorbitity interfering with safe collection of blood

• Having objectives against coded storage of tissue

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	20-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL73648.091.20

Study results

Date completed: 17-04-2023

Actual enrolment: 10

Summary results
Trial is onging in other countries