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COVID-19 revaccination of hematology patients after cell therapy or B-cell-depleting immunochemotherapy

Submission date
17/04/2024

Recruitment status
Recruiting

Registration date
28/10/2024

Overall study status
Ongoing

Last Edited
28/10/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Current guidelines in The Netherlands and abroad advise revaccination for patients who were B cell depleted at the time of the primary COVID-19 vaccination series and for patients who received a hematopoietic cell transplantation (HCT) (bone marrow transplant) after the primary COVID-19 vaccination series. It is advised to revaccinate with three doses of a mRNA vaccine given 4 weeks apart, followed by a booster vaccination over 3 months later, although data substantiating this schedule are lacking. In order to design revaccination schedules for hematology patients who lost protective immunity against COVID-19 after HCT, or who were B cell depleted after they had received vaccination, we need to investigate who needs to be revaccinated and how many vaccinations are necessary.

Who can participate?
The following patient groups are advised to be revaccinated and will be eligible for enrolment in this study:
Group 1: Patients who received B-cell-depleting immunochemotherapy or B-cell-depleting CAR T cell therapy (CD19 directed)
Group 2: Patients who received autologous HCT after myeloablative chemotherapy for multiple myeloma (myeloablative chemotherapy: high dose melphalan [HDM]) or non-Hodgkin or Hodgkin lymphoma (myeloablative chemotherapy: BCNU-etoposide-Ara-C-Melphalan [BEAM] or BCNU-thiotepa)
Group 3: Patients who received allogeneic HCT

What does the study involve?
Patients will be revaccinated against COVID-19 as part of the standard of care regarding revaccination after cell therapy or B-cell-depleting immunochemotherapy. Patients give blood samples at each vaccination timepoint and also additional timepoints to evaluate responses to COVID-19 revaccination.

What are the possible benefits and risks of participating?
The risks of this study are negligible to none. Only mild bruising after blood draws. There are no

direct benefits for patients participating in this study. However, patients will be informed about their antibody concentrations after they have been measured.

Where is the study run from?
Amsterdam UMC (Netherlands)

When is the study starting and how long is it expected to run for?
October 2023 to December 2026

Who is funding the study?
ZonMw (Netherlands)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
NL85613.018.23

Study information

Scientific Title
COBRA re-KAI study: COVID-19 vaccination in patients with reduced B-cell and T-cell immunity: response after re-vaccination of a kaleidoscopic group of hematological patients: what's the impact?

Acronym
COBRA re-KAI

Study objectives
Current guidelines in The Netherlands and abroad advise revaccination for patients who were B-cell-depleted at the time of the primary COVID-19 vaccination series and for patients who received an autologous or allogeneic hematopoietic cell transplantation (HCT) after the primary COVID-19 vaccination series. It is advised to revaccinate with three doses of a mRNA vaccine given 4 weeks apart, followed by a booster vaccination >3 months later, although data substantiating this schedule are lacking. In order to design revaccination schedules for hematology patients who lost protective immunity against COVID-19 after HCT, or who were B cell depleted after they had received vaccination, researchers want to investigate how many revaccinations against COVID-19 are needed to restore immunity. They hypothesize that a substantial part of the study group does not require a complete COVID-19 vaccine schedule.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 19/02/2024, METC, Amsterdam UMC (Meibergdreef 9, Amsterdam, 1105 AZ, Netherlands; +31 (0)204445585; metc@amsterdamumc.nl), ref: 2023.0951

Study design
Observational cohort study

Primary study design
Observational

Study type(s)
Prevention, Efficacy

Health condition(s) or problem(s) studied
Hematology patients eligible for COVID-19 revaccination after cell therapy or B-cell-depleting immunochemotherapy

Interventions
Observational cohort study among 250 hematology patients categorized into five different groups (n = 50 per group). All participants will receive three mRNA COVID-19 vaccination doses 4

weeks apart, followed by a booster vaccination >3 months later, per the Dutch guidelines. Cellular and humoral immunity will be measured at baseline (the day of the 1st vaccination), at 28 days after each vaccination and at 7 days after the first vaccination.

T0 = Baseline of study and first vaccination of revaccination schedule
T1 = Blood sampling 7 days after the first revaccination to test for recall responses.
T2 = 28 days after Revaccination 1, also Day 0 of the second vaccination.
T3 = 28 days after Revaccination 2, also Day 0 of the third vaccination.
T4 = 28 days after Revaccination 3
T5 = Booster vaccination day 0 and +6 months after the start of the primary schedule
T6 = 28 days after Booster vaccination.

The total duration of the study is 7 months.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
mRNA COVID-19 vaccine

Primary outcome(s)
1. Cellular antigen specific B and T cell responses. These will be measured with AIM (activation-induced marker) assays using flow cytometry. Humoral responses expressed in antibody concentration (BAU/ml), avidity, neutralization (expressed as ID50)) and SARS-CoV-2 specific immunity. Humoral responses will be measured by using bead-based multiplex immune assay against subunit 1 (S1), receptor binding domain (RBD), and nucleocapsid (N) antigen domains of SARS-CoV-2 determined quantitatively and centrally. Neutralization will be tested using lentiviral-based pseudoviruses expressing SARS-CoV-2 variants. Measured prior to the start of the revaccination schedule.
2. SARS-CoV-2 antibody concentrations measured using bead-based multiplex assays at 28 days after each revaccination. After the first vaccination the researchers will also measure antibody concentration 7 days after vaccination.
3. The number of revaccinations needed for each patient group to reach sufficient SARS-CoV-2 antibody concentrations (compared to average antibody concentrations obtained in healthy individuals after the primary series of 2 vaccinations followed by a booster vaccination), measured using bead-based multiplex assays at T0, T1, T2, T3, T4, T5 and T6.

Key secondary outcome(s))
1. Day 7 antibody concentrations correlated with pre-revaccination, and day 28 post-vaccination, cellular and humoral immunity, as a measure of residual immunity. Measured using bead-based multiplex assays.
2. Humoral and cellular immunity 28 days after each vaccination, measured using FACS analysis and bead-based multiplex assays.
3. B-cell maturation measured by avidity test/indices, (clonal) antigen-specific B cell analysis and antibody glycosylation prior to and 28 days after each vaccination.
4. The cellular immune response by cytokine production and expression of activation and exhaustion markers on CD4 and CD8 T cells prior to and 28 days after each vaccination, measured using FACS analysis.

5. Cellular and humoral SARS-CoV-2 specific immunity 5 months after the 3rd vaccination, measured using FACS analysis and bead-based multiplex assays.
6. Immune parameters (e.g. peripheral blood B and T cell numbers, IgG concentrations) associated with cellular and humoral responses to COVID-19 re-vaccination, measured by the immunological laboratory with FACS analysis.
7. Clinical parameters (e.g. hematologic diagnosis, current and past therapies including immunosuppressive drugs, date of last therapy) associated with responses to COVID-19 re-vaccination, measured using the Castor database which includes clinical parameters from patient files at all timepoints.
8. The effect of previous SARS-CoV2 infection on COVID-19 re-vaccination responses, type of measurement to be determined at later date. Will include subjects that contract COVID-19 during the study and will be studied with appropriate tests.
9. Serious adverse events (SAE) <7 days after each COVID-19 re-vaccination, reported yearly using a line listing since there are minimal risks associated with the study. They will report to the medical ethical testing committee as prescribed by the definitions of the METC.
10. SARS-CoV-2 breakthrough infection and severity (including death) after COVID-19 re-vaccination, measured using the Castor database, which will contain a short questionnaire on SARS-CoV-2 infection and severity.

*Note that this study is also biobanking the majority of its collected material to use for in-depth immunological assays at a later date which have not been established at the present time.

Completion date
31/12/2026

Eligibility

Key inclusion criteria
Age ≥18 years

Group 1: Patients who received:
1. B cell depleting immunochemotherapy (n = 50), at least 8 months after the last B-cell depleting therapy before the first vaccination
2. B cell depleting CAR T cell therapy (n = 50); 3 months after treatment

Group 2: Patients who received autologous HCT for:
1. Multiple myeloma (myeloablative chemotherapy: high dose melphalan [HDM]) (n = 50); 3 months after treatment before the first vaccination
2. Non-Hodgkin or Hodgkin lymphoma (myeloablative chemotherapy: BCNU-etoposide-Ara-C-Melphalan (BEAM) or BCNU-thiotepa) (n = 50); at least 3 months after transplantation with a maximum of 6 months before the first vaccination

Group 3: Patients who received allogeneic HCT (various indications) (n = 50) 3 months after transplantation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Key exclusion criteria
1. Unwilling or unable to give informed consent
2. Known allergy to one of the components of the vaccine
3. Patients with a life expectancy of <12 months

Date of first enrolment
01/05/2024

Date of final enrolment
01/12/2026

Locations

Countries of recruitment
Netherlands

Study participating centre
Amsterdam UMC
Meibergdreef 9
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1105 AZ

Study participating centre
UMCG Groningen
Hanzeplein 1
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Sponsor information

Organisation
Amsterdam University Medical Centers

ROR
https://ror.org/05grdyy37

Funder(s)

Funder type
Research organisation

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date