Cellular and Serological Immune Response Monitoring in SARS-CoV2-infected individuals, without need of hospitalization

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26590

Source
NTR

Brief title
SARS-RESPONSE control study

Health condition

SARS-CoV2 infection

Sponsors and support

Primary sponsor: Leiden University Medical Center
Source(s) of monetary or material Support: Not applicable

Intervention

Outcome measures

Primary outcome

Dissection of the cellular and serological immune response against SARS-CoV2 with special

attention for SARS-CoV2 specific T-cell & B-cell responses (including plasma cell and memory B-cell responses) and antibody formation against viral proteins as well as for innate inflammatory mediators. This includes the assessment of the primary (naïve) T-cell and B-cell repertoire as basis for the adaptive immune response against the new antigenic epitopes of SARS-CoV2 and the detailed mapping of innate and inflammatory mediators, fully in line with the analyses in patients of the BEAT-COVID-1 “sister” protocol.

Secondary outcome

Secondary objective 1: Single cell sequencing of immunoglobulin (IG) genes of SARS-CoV2-specific plasma cells and memory B-cells with special attention to anti-Spike antibodies and their capability to block viral binding to human ACE2 proteins.
- Secondary objective 2: Cloning and expression of the selected IG genes for in-depth studies on antibody reactivity, particularly epitope mapping and affinity studies.
- Secondary objective 3: Immune profiling of nasal mucosal immune responses.
- Secondary objective 4: Single cell T-cell receptor (TR) gene sequencing of SARS-CoV2 specific CD4+ and CD8+ T-cells and characterization of dominant T-cell epitopes.
- Secondary Objective 5: Sequencing of the viral Spike protein, being a major target of neutralizing antibodies, for mutant analysis, in relation to antibody responses (1).
- Secondary objective 6: Assessment of activation of the coagulation system and complement system in parallel to the immune response.
- Secondary objective 7: Sequencing of ACE2 and immune-related genes of the same individuals to understand the potential presence and meaning of polymorphisms.

Study description

Background summary

Background of the study
The ongoing SARS-CoV2 pandemic is has been spreading rapidly, spreading with significant differences between affected individuals., which These differences are not yet well understood. Infected individuals show a wide array of clinical symptoms ranging from asymptomatic or a mild disease course to severe clinical disease requiring mechanical ventilation in 2 to 3% of cases. Differences in viral dosage and circumstances of exposure might play a role, but this does not explain the higher vulnerability of older people and the very low frequency of COVID-19 at young age. Little is known about the underlying risk factors for severe disease other than older age, although an association with cardiovascular disease, diabetes mellitus and obesity has been reported. The ongoing BEAT-COVID-1 study (ABR no. NL73740.058.20) is focusing on in-depth immune and inflammatory responses in hospitalized patients, both at COVID departments and at Intensive Care Units (ICU).
The study presented here focusses on the dissection of the stepwise cellular and serological immune response in infected individuals with a subclinical or mild disease course, not requiring hospitalization. The results of this study will be compared with the results obtained from the BEAT-COVID-1 study. Understanding differences in immune response against SARS-

CoV2 will elucidate why the disease course can be so heterogeneous.

Objective of the study
Primary objective: Dissection of the cellular and serological immune response against SARS-CoV2 with special attention for SARS-CoV2 specific T-cell & B-cell responses and antibody formation against viral proteins as well as for innate inflammatory mediators.
- Secondary objective 1: Single cell sequencing of immunoglobulin (IG) genes of SARS-CoV2-specific plasma cells and memory B-cells with special attention to anti-Spike antibodies and their capability to block viral binding to human ACE2 proteins.
- Secondary objective 2: Cloning and expression of the selected IG genes for in-depth studies on antibody reactivity, particularly epitope mapping and affinity studies.
- Secondary objective 3: Immune profiling of nasal mucosal immune responses.
- Secondary objective 4: Single cell T-cell receptor (TR) gene sequencing of SARS-CoV2 specific CD4+ and CD8+ T-cells and characterization of dominant T-cell epitopes.
- Secondary Objective 5: Sequencing of the viral Spike protein, being a major target of neutralizing antibodies, for mutant analysis, in relation to antibody responses (1).
- Secondary objective 6: Assessment of activation of the coagulation system in parallel to the immune response.
- Secondary objective 7: Sequencing of ACE2 and immune-related genes of the same individuals to understand the potential presence and meaning of polymorphisms.

Study design
In order to achieve the primary objective and the secondary objectives, a prospective observational cohort study is proposed in otherwise healthy individuals (n=10), who have become infected with the SARS-CoV2 virus (= tested positive by SARS-CoV2 PCR testing of nasal swab, throat swab and/or sputum). They might have minor or mild clinical symptoms, not requiring hospitalization. See figure 1 in the study protocol for an extensive description of the study design.

Study population
The study population consists of 10 adult subjects, tested positive for SARS-CoV2 and without need for hospitalization. The 10 subjects will be recruited among LUMC personnel, living in Leiden or direct environment (e.g. within 10 km from LUMC), allowing for traveling by car, bike or by walking to LUMC (no public transportation).

Primary study parameters/outcome of the study
Absolute counts (relative counts) with comparison to well-defined age-matched reference values. Based on the first results of the BEAT-COVID-1 “sister study”, and the ongoing clinical trials of the Innovative Medicines Initiative (IMI) PERISCOPE program, we expect clear kinetic differences as compared to age-matched reference values. Comparison between the BEAT-COVID-1 results and the newly obtained results from this study will potentially explain the reason of the delays in the antigen-specific immune response in the COVID patients.

Secundary study parameters/outcome of the study (if applicable)
High throughput sequencing of IG genes (both IGH and IGK-IGL) at the single cell level of expanded plasma cells and antigen-specific memory B-cells at consecutive time points in blood. In parallel, the B-cell compartment in selected nasal scrapes will be evaluated. The

transcribed and expressed IGH isotype usage will be assessed in combination with the full sequence of the V(D)J exons of both IGH and IGK-IGL genes.
The obtained IG sequences will be mapped against our new “population-matched IG” (pmIG) data base, which we have developed over the last two years. This is the first IG database that consists of true genuine germline genes only. This database is essential to understand how many SHM-induced mutations might have occurred in the anti-SARS-CoV2 antibodies and to what extend the number and their position differ within and between the subjects of this study and in comparison with the COVID patients of the BEAT-COVID-1 projectstudy. These comparative studies will most likely unravel how “fast and easy” antibodies can be raised in healthy subject compared to COVID patients, where antibody development seems to be seriously delayed and impaired, suggesting more complex SHM and selection mechanisms.
In parallel, the TR genes of blood T-lymphocytes and nasal scrapes will be sequenced to evaluate whether the same or distinct antigen-specific T-cell responses can be detected in blood and nasal scrapes. This may unravel which T-cell immune response is most beneficial for eliminating the SARS-CoV2 virus.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable)
The burden of the study is limited and related to a maximum of 14 donations of small volumes of blood, nasal swabs, nasal lining fluid (nasosorption filter) and (optionally) 5 times a nasal inferior turbinate scrape.
The risk of harm is very low. Risks related to venous puncture are slight pain at puncture site and a hematoma. The amount of blood drawn during the first week is maximally 90.5 mL, during the first 6 weeks maximally 242 mL, and during the full period of follow-up (6 months) maximally 294 mL , based on a maximum duration of SARS-CoV2 positivity of 2 weeks. It is expected that most subjects will be symptom-free and SARS-CoV2 negative within 2 weeks after inclusion, implying that generally a total of less than 294 mL will be collected over a period of 6 months.
Albeit that nasal scrapes have not been studied in patients with airway infections, no epistaxis was reported in earlier trials with in total approximately 1,000 healthy donors (incidence < 0.1% based on experience; and personal communication with S. Jochems). We anticipate that the nasal mucosa during infection could be more vulnerable and will not perform this in patients with a history of epistaxis.

Study objective

We aim to study the SARS-CoV2 infection/disease course via dissection of the cellular immune response in blood, with special attention to antigen-specific T-cells and B-cells and antibody formation against viral proteins, particularly blocking (=neutralizing) anti-Spike antibodies. These results will be compared with the results obtained from more severe patients recruited and studied in the BEAT-COVID-1 study, to understand whether differences in the T-cell and B-cell immune responses can explain the heterogeneity in disease course. In addition, characterization of SARS-CoV2 specific T-cell and B-cell response in the patients with non-severe vs. severe disease will provide important information on what determines an effective immune response, and will be important for therapy design and will facilitate evaluation of vaccine candidate immunogenicity

Study design

During first 2 to 3 weeks (SARS-CoV2 positivity) samples will be taken on day 0, 1, 3, 5, 8, 10, 12, 15, 17, and 19. As soon as the subjects are symptom-free and have 2 consecutive nasal swabs tested negative, samples will be taken on wk 0, 1, 3, 9 and 23.

Intervention

No interventions

Contacts

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Eligibility criteria

Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:
• Subject (male or female) tested positive for SARS-CoV2 by PCR (nasal swab, throat swab and/or sputum);
• Subject is an adult of 18-65 years old;
• Subject is able to understand the PIF document, written in Dutch;
• Subject is able to communicate well with the investigator in the Dutch language;
• Subject signed informed consent prior to any study-mandated procedure;
• Subject is living in Leiden or direct environment (e.g. within 10 km from LUMC), allowing for traveling by car, bike or by walking to LUMC (no public transportation).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Subject tested negative upon SARS-CoV2 PCR re-analysis of nasal swab at intake;
• Subject previously fainted before, during or after a medical procedure with needles;
• Subject received plasma or other blood products during the previous 3 months;
• Subject received a vaccination during the previous 3 months;
• Subject is obese with BMI ≥30, based on provide weight and length information;
• Subject has a pre-existing coagulopathy;
• Subject uses medication for a coagulopathy;
• Subject uses medication that suppresses the immune system;
• Subject has an auto-immune disease or another immune disease;
• Subject has another infection in addition to the SARS-CoV2 infection;
• Subject participated in a clinical trial within 6 months prior to this study;
• For women: subject is pregnant or is providing breast-feeding.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2020
Enrollment:	10
Type:	Actual

IPD sharing statement

Plan to share IPD: Yes

Plan description
The results of the study will be published in scientific manuscripts

Ethics review

Positive opinion

Date:	01-07-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50071
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8745
CCMO	NL74062.058.20
OMON	NL-OMON50071

Study results