Deciphering Long-COVID: Uncovering the Significance of Immunological & Virological Dysregulation Underpinning Long-COVID Pathophysiology (DECI-LOCO Study)

Published: 30-11-2023
Last updated: 27-12-2024

Primary Objective:Our primary objective is to generate in-depth immune profiles, which include phenotypic and functional analyses, as well as epigenetic and transcriptomic analyses, of several B cell, T cell, and monocyte subsets, which relate to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON56085

Source
ToetsingOnline

Brief title
DECI-LOCO study

Condition

- Autoimmune disorders
- Respiratory tract infections

Synonym
Long-COVID

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Epigenetics, Immune-dysregulation, Long-COVID, Viral-persistence

Outcome measures

Primary outcome

Percentage of age-associated B cells (ABCs; CD21loCD11c+ DN B cells) in peripheral blood mononuclear cells (PBMCs) from long-COVID patients, compared to convalescent, phenotypic, and autoimmune controls.

Secondary outcome

Immunological profile

The quantification of ABCs as primary parameter will be part of the immunological profiling of long-COVID patients. This will be accompanied by the characterization and quantification of several other parameters of circulating lymphoid (B and T cell) and myeloid (monocytes and dendritic cells) populations. Frequencies as well as the activation status of different subsets will be determined in PBMCs from both patients and controls. In addition, the expression of several activation markers (including CD86, MHC-II, CD69, etc.) and exhaustion markers (PD-1, CTLA-4, etc.) will be determined. Functional experiments will be conducted on B and T cells to measure B and T cell receptor (BCR and TCR, respectively) signaling responsiveness. In addition, the cytokine production potential will be evaluated in lymphoid and myeloid subsets to assess functionality. Differences in the potential of cytokine production in

specific cell subsets between groups will be translated to a systemic level, by quantifying circulating cytokine concentrations in plasma/serum. Quantification and phenotypic assessment of SARS-CoV-2-specific B and T cells will be performed using in-house techniques developed at the Department of Viroscience [26]. Cell populations of interest will be further investigated on a transcriptional and epigenetic level, using RNA- and ATAC-seq, respectively. Finally, immunological characteristics will be combined and correlated with clinical parameters to form computationally-calculated immunological profiles.

Virological profile

A virological profile will be created based on several circulating virological factors. For SARS-CoV-2, these include the quantification of circulating RNA and spike protein in serum/plasma. For reactivation of latent viruses, these include the quantification of viral load of EBV, CMV, and HHV6 in serum/plasma. Concentrations and neutralization capacity of antibodies (IgM and IgG) against both SARS-CoV-2 and other latent viruses (anti-EBV, anti-CMV, and anti-HHV6) will be determined in serum/plasma. Based on previous findings, SARS-CoV-2 protein will also be detected and quantified in circulating monocyte subpopulations. Finally, these virological characteristics will be combined and correlated with clinical parameters to form a computationally-calculated virological profile.

Patient reported outcome measures

1] Persisting symptoms and severity (corona symptom checklist)

2] Health-related quality of life (HRQoL, EQ5D)

3] Fatigue (Fatigue Assessment Scale, FAS)

4] Dyspnea (Modified Medical Research Council Dyspnea Scale, mMRC)

5] Cognitive failures in daily life (Cognitive failure questionnaire, CFQ)

6] Return to work (iMTA Productivity Cost Questionnaire, iPCQ)

7] Post-Exertional Malaise (modified sf-DSQ-PEM)

8] Postural orthostatic tachycardia syndrome (Malmo POTS symptom score)

9] Recovery status (Numeric scale and Likert scale)

Study description

Background summary

After recovery of the acute phase of COVID-19, a significant proportion of patients suffer from persistent symptoms, known as long-COVID. This leads to chronic disability and reduced quality of life. Because the underlying causes of long-COVID are unclear, there are currently no treatments available. It is found that several abnormalities, including a dysregulated immune system, an abnormal anti-viral response and viral persistence, and reactivation of latent human herpes viruses (HHVs) may contribute to the development of long-COVID. However, how these abnormalities lead to disease pathogenesis is unknown. Therefore, in this project we will investigate these abnormalities in more detail, and link biological data to clinical symptoms, including fatigue, shortness of breath, muscle aches, headaches, and loss of concentration. Together, this will bring us closer to understanding the causes of long-COVID. It will allow us to stratify patients based on these biological components and will enable us to find possible treatment options for different patient groups.

Study objective

Primary Objective:
Our primary objective is to generate in-depth immune profiles, which include phenotypic and functional analyses, as well as epigenetic and transcriptomic analyses, of several B cell, T cell, and monocyte subsets, which relate to immune activation/dysfunction in patients with long-COVID, and to link these to clinical parameters. In the lymphoid compartment, B and T cell subsets, including virus specific T cells, will be analyzed for shifts in subsets, as

well as alterations in activation and/or exhaustion phenotype. B and T cell receptor signaling will be assessed, as well as cytokine production by monocytes and lymphocytes. Observed alterations in specific circulating lymphocyte or monocyte subsets can be further analyzed on transcriptomic and epigenetic level, using RNA-sequencing (seq) and ATAC-seq, respectively. All observed alterations will be combined to form unique immune profiles to discover possible disease-underlying mechanisms, as well as possible targets for therapy.

Secondary Objective:
Our secondary objective is to generate in-depth virological profiles, to link aberrations in viral responses or reactivation to clinical parameters. To explore the possibility that chronic immune activation and dysregulation are caused or supported by viral persistence, we will measure presence of SARS-CoV-2 spike protein in serum and specific monocyte populations [22]. Also, we will determine the profile of SARS-CoV-2-specific B and T cells, and antibodies present in the circulation of included subjects. We will determine the breadth of the antibody response by measuring total antibody concentrations and virus-neutralizing capacity against SARS-CoV-2. To explore whether chronic immune activation may be caused by a reactivation of latent viruses, we will determine virus titers of EBV, CMV, and HHV6 in serum/plasma. To link virus reactivation to the presence of circulating virus-specific antibodies, we will also determine antibody titers against these latent viruses.

Study design

This study will be a comparative, non-randomized, observational study. Recently doctor-diagnosed long-COVID patients (<1 year) and long-term ill long-COVID patients (> 2 years), after PCR or antigen test confirmed initial COVID infection (WHO long-COVID definition) will be compared with convalescent controls (CCs).

Study burden and risks

For this study, blood samples will be drawn, of which the risk is minimal. However, it can cause mild discomfort. This study aims to unravel the pathophysiology of long-COVID and thus contributes to improve treatment in the future.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Long-COVID patients
• Age >= 18 years, <65 years
• Past COVID-19 diagnosis, based on
o Positive PCR
o Positive Sars-Cov2 serology
o Positive rapid antigen test
o Typical clinical syndrome during the first pandemic wave, when testing was not possible
• Long-COVID-19 diagnosis based on World Health Organisation consensus diagnosis (*Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time)*.
o Ref https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
• Overall functioning <70% compared to functioning prior to onset of

Long-COVID/ COVID-19 infection
• Presence of post-exertional malaise
• Provided written informed consent

CC
• Age >= 18 years, <65 years
• Past COVID-19 diagnosis, based on
o Positive PCR
o Positive Sars-Cov2 serology
o Positive rapid antigen test
o Typical clinical syndrome during the first pandemic wave, when testing was not possible
• No diagnosis of long-COVID, good recovery. Overall functioning >95% compared to functioning prior COVID-19 infection
• Self-reported general good wellbeing
• Provided written informed consent

Exclusion criteria

Long-COVID patients
• Unable or not willing to provide written informed consent
• Unable to complete written questionnaires in Dutch
• Unable to draw blood for study purposes
• Diagnosis of dementia
• Active treatment with hyperbaric oxygen treatment during study start
• Alternative diagnosis that may explain clinical symptoms
• No re-infection with COVID-19 in the past 3 months
• Suffering from any pre-existing immune-driven disease or use of anti-inflammatory therapy of any kind (including NSAIDs and steroids) during the last 3 months
•

CC
• Unable or not willing to provide written informed consent
• Unable to complete written questionnaires in Dutch
• Unable to draw blood for study purposes
• Diagnosis of dementia
• Genetically related to participating patients (e.g. brother/sister/parent)
• Suffering from any immune-driven disease or use of anti-inflammatory therapy of any kind (including NSAIDs and steroids), including during the last 3 months
• Re-infection with SARS-CoV-2 in the past 3 months.
• Unable or not willing to provide written informed consent
• Unable to complete written questionnaires in Dutch

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-12-2023
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	30-11-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL85275.078.23