Characterization of aberrant immune response in post-COVID using innovative signal transduction pathway technology (LC-STP)

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Research objective: Transcriptome data from main immune cell types (monocytes, CD4+ and CD8+ T cells, B-cells, NK cells) of post-COVID patients are analyzed using STP technology. STP-activity results are interpreted in combination with clinical...

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

Summary

ID

NL-OMON56864

Source
ToetsingOnline

Brief title
Immune cell STP*s to characterize Long-COVID

Condition

- Immune disorders NEC
- Viral infectious disorders

Synonym
Long-COVID, Post-COVID

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Immune cells, Long-COVID, Signal transduction pathways (STP)

Outcome measures

Primary outcome

Transcriptome analysis by STP technology delivers a an STP activity score for 15 STPs, for each analyzed immune cell type sample (CD4+ T-, CD8+ T-, B-lymphocytes, NK cells, monocytes). The main study parameters are the STP activity score of 15 STP pathways of the 5 types of immune cells. The main goal is to compare STP activity between long-COVID and controls.

Secondary outcome

We will biologically interpretate the abnormal immune function/ STP activity profile in individual long-COVID patients followed by identification and description of potential STP drug targets by DCDC-Tx.
If applicable, we will assess for long-COVID subtypes, based on interpretation of STP results (regarding differential immune cell dysfunction and treatment targets) in combination with clinical and/or other laboratory parameters.
Several biomarkers implicated in long-COVID and related to immune dysregulation will be measured in serum (including but not limited to) cortisol, cytokines (primarily CCL2, CCL11, galectin-1, galectin-9, IL-6, IL-8, IL-10, CXCL10 and sCD163 (a macrophage activation marker).

Study description

Background summary

An aberrant immune response is considered to play an important role in post-COVID. Characterization of the immune response is an essential first step in development of therapy. A validated unique RNA-analysis-based technology is used to measure activity of 15 crucial cellular processes (Signal Transduction Pathways, STPs). Preliminary results in a small study by DCDC already showed abnormal STP activity in monocytes from post-COVID patients. The study will be performed by the highly experienced team from Erasmus MC and DCDC, supported by C-Support, Post-COVID-NL and Post-COVID Foundation. Information on abnormally active STPs forms the basis for subsequent therapy development by DCDC, making use of FDA-approved drugs (>20K). DCDC has evidence that STP technology can be applied to identify clinically effective drugs. Information on STP technology and publications: https://DCDC-Tx.com.

Study objective

Research objective: Transcriptome data from main immune cell types (monocytes, CD4+ and CD8+ T cells, B-cells, NK cells) of post-COVID patients are analyzed using STP technology. STP-activity results are interpreted in combination with clinical parameters to define the aberrant immune response in post-COVID patients, as basis for future drug development.

Study design

1. Selection of 25 post-COVID patients and 25 control patients recovered from acute Covid infection, making use of the clinical patient database established by Merel Hellemons.
Blood withdrawal at out-patient clinic. Clinical annotation of selected patients.

2. Blood sampling from selected group at outpatient clinic. Expected sample number: n= 50 (patients + controls), 5 immune cell types per patient, total 250 samples for analysis.
Blood sampling; immune cell separation into immune cell subsets using FACS-based sorting : CD4+ and CD8+ T cells; NK cells, B cells, monocytes; RNA extraction, RNAseq transcriptome measurement using Illumina NGS (alternatively Affymetrix microarrays), sample storage.
In addition cortisol, cytokines (IL-6, IL-10, TNF-alfa, Galectin-9, CCL2, CXCL10) and sCD163 (macrophage activation marker) will be measured in plasma.
3. STP technology analysis of transcriptome data to determine quantitative STP activities per cell sample; identification of normal range of STP activity in control individuals; identification of abnormal STP activity for each

individual post-COVID patient and resulting mechanism of immune system dysfunction; identification of potential subgroups.
4. Coupling of clinical annotation to STP analysis results (immune dysfunction) per patient. Identification of potential sybtypes (based on clinical data, STP and other blood measurements).

Study burden and risks

The questionnaires to be completed and the blood collection as part of the study are minimally stressful. The questionnaires can be completed at home, if required paused and completed over a longer period of time. The blood collection may hurt a little or cause bruising, but the collection is carried out by an experienced researcher or doctor to ensure that it runs as smoothly as possible. To make the visit as hassle-free as possible, the sampling location is close to the parking garage. Wheelchairs are available.

Contacts

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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 Organization 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_COVID19_condition-Clinical_case_definition-2021.1
• Overall functioning <70% compared to functioning prior to onset of Long-COVID/ COVID19 infection
• Presence of post-exertional malaise
• Provided written informed consent
• Long COVID symptoms present > 6 months

Healthy controls
• 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 clinical 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
• Alternative diagnosis that may explain their clinical symptoms
• Re-infection or booster vaccination 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

Healthy controls
• 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 or booster vaccination in the past 3 months.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-08-2024
Enrollment:	50

Type:	Actual

Ethics review

Approved WMO Date:	04-07-2024
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	NL86227.078.24