TURN-COVID Biobank: The Dutch cohort study for the evaluation of the use of neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2

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This study has been transitioned to CTIS with ID 2024-515263-60-00 check the CTIS register for the current data. - A. What are the SARS-CoV-2 viral load kinetics during and after treatment with neutralizing monoclonal antibodies and other antiviral...

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

Summary

ID

NL-OMON52215

Source
ToetsingOnline

Brief title
TURN-COVID

Condition

- Viral infectious disorders

Synonym
COVID-19, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Antiviral agents, COVID-19, Monoclonal antibodies

Outcome measures

Primary outcome

- A. What are the SARS-CoV-2 viral load kinetics during and after treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?

- B. What is the risk of SARS-CoV-2 infection after prophylactic use of monoclonal antibodies or other antiviral agents?

- C. Do viral variants, spike mutations and immune escape occur during treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?

- D. What are the viral antibody and inflammatory response kinetics during and after treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?

Secondary outcome

- Not-applicable

Study description

Background summary

2. INTRODUCTION AND RATIONALE

New SARS-CoV-2 specific therapies
From the beginning of the worldwide pandemic till now no effective specific anti-SARS-CoV-2 treatment was available1,2. In June 2021 the use of SARS-CoV-2 monoclonal antibodies as early treatment for SARS-CoV-2 infected individuals became available in the Netherlands after an emergency use authorisation of the FDA and EMA. First large phase-III randomised controlled clinical trials have showed that SARS-CoV-2 monoclonal antibodies, when given early after the onset of symptoms, bind the SARS-CoV-2 spike protein effectively and prevent hospital admission and death3-7. Additionally, promising SARS-CoV-2 compounds such as the oral antivirals molnupiravir8,9 and nirmatrelvir/ritonavir10 recently received an emergency use authorization of the FDA in patients with Covid-19 at high risk of hospitalization and death. EMA's human medicines committee (CHMP) has also started a rolling review of the oral antiviral medicine molnupiravir and gave an emergency auhorisation for nirmatrelvir/ritonavir. Recently, the EMA gave an emergency authorization for and tixagevimab/cilgavimab for the prevention of COVID-19 before potential exposure to the SARS-CoV-2 virus11.

Pathophysiology
SARS-CoV-2 monoclonal antibodies
SARS-CoV-2 monoclonal antibodies recognize a single and unique epitope on the SARS-CoV-2 spike proteins and are derived from donor B-lymphocytes. The donor B-lymphocytes can be derived either from patients who had Covid-19 or humanized mice who were exposed to SARS-CoV-23,12. The SARS-CoV-2 monoclonal antibodies inhibit the entry of the virus into the host cells (neutralization).
Furthermore, antibody binding results in opsonization and is the first step of phagocytosis, eventually resulting in apoptosis and necrosis of the infected cells3. Monoclonal antibodies can be altered artificially in the laboratory to combat emerging variants of SARS-CoV-23. Frequently investigated combinations are casirivimab with imdevimab, sotrovimab and balanivimab with etesevimab4-7,13. Tixagevimab/cilgavimab (Evusheld) is the first monoclonal antibody authorised by the EMA for the prevention of COVID-1911

Oral anti-SARS-CoV-2 agents
At present, many candidate small-molecule therapeutics have been developed that can inhibit both the infection and replication of SARS-CoV-2 and even potentially relieve cytokine storms and other related complications. As SARS-CoV-2 infects cells, reproduces itself, and spreads, the coronavirus relies on dozens of viral and host proteins to complete its life cycle. The new oral pill nirmatrelvir/ritonavir (Phizer) inhibits the main viral protease used to create other proteins for the virus10. The oral pill molnupiravir (Merck) inserts a defective RNA building block when the virus uses an enzyme known as a polymerase to copy its genome.8

The role of new SARS-CoV-2 therapies
There are a number of factors that most probably will lead to seasonally peaks of infection and hospital admissions for SARS-CoV-2 infections14-16. First, there will remain a group within our population that remains willingly

unvaccinated. Second, it is shown that numerous immunocompromised patients have inadequate antibody response to vaccinations and do not produce long-term protection17,18. At last, with new emerging viral variants arising with expected higher viral spread, it is assumed that outbreaks of SARS-CoV-2 infections will remain prevalent in the coming years14-16,19.
With regard to immunocompromised patients, even with the most effective mRNA SARS-CoV-2 vaccines show reduced or even absent humoral responses in patients with solid organ transplants or for instance in patients treated with anti-CD20 for an hematologic malignancy17,18. The fact that immunocompromised patients have inadequate immune response to vaccinations underscores the need of treatment options essential for a subpopulation to slow or stop the replications of the SARS-CoV-2 virus. Especially for these immunocompromised patients the novel SARS-CoV-2 therapies could become a real game changer.

First results of phase-III studies
SARS-CoV-2 monoclonal antibodies
The first results of several phase III placebo-controlled randomized controlled clinical trials of monoclonal antibodies of SARS-CoV-2 are now available4,5,7,13. The studies were designed to analyze the effect of these monoclonal antibodies when given early after symptom onset to prevent disease progression, hospital admission and mortality. Two other studies presented the interim analysis regarding the treatment of casirivimab with imdevimab4 combination and the sotrovimab alone5. These two studies investigated a single intravenously administration of monoclonal antibodies within 3-7 days after the start of symptoms and demonstrated a relative reduction of 70-85% in Covid-19 related hospital admission and death within four weeks4,20.

Due to the abovementioned evidence, the Dutch medical guideline for the treatment of SARS-CoV-2 patients updated on July 2022. The Dutch Working Party on Antibiotic Policy (Stichting Werkgroep AntibioticaBeleid, SWAB) now considers to treat high-risk patients, with or without a prior antibody response (that means no vaccination response and no seroconversion) and with a high risk of Covid-19 disease progression to start treatment with neutralizing monoclonal SARS-CoV-2 antibodies and oral antiviral agents (nirmatrelvir/ritonavir) 21. Patients with a high risk to develop severe Covid-19 are defined as follows in the Dutch guidelines:

Post organ or bone marrow/stem cell transplantation, hematological malignicany, solid tumor <= 3 months chemotherapy or immunotherapy; severe kidney failure/dialysis, primary immunodeficiency, using immunosuppressive medication21,22.

At the moment (July 2022), there are no SARS-CoV-2 monoclonal antibody agents available in the Netherlands which have potent neutralisation against the dominant B.1.1.529 (Omicron) variant of concern (VOC). However, tixagevimab/cilgavimab (Evusheld) will become available in the Netherlands in Q3, 2022. The EMA evaluated data from a study in over 5,000 people showing that

Evusheld, given as two injections of 150 mg tixagevimab and 150 mg cilgavimab, reduced the risk of COVID-19 infection by 77%, with the duration of protection from the virus estimated to be at least six months11.

Oral anti-SARS-CoV-2 agents
The mechanism of action of the nucleoside analogue molnupiravir and the protease inhibitor nirmatrelvir/ritonavir are independent of mutations in the spike protein, which can affect the efficacy of monoclonal antibody treatments. The first results of a phase III placebo-controlled randomized controlled clinical trials of molnupiravir are now available9.
Both oral antivirals are developed to be taken within the first few days of Covid-19 infection and are reported to reduce the risk of hospitalization and death by approximately 30% for molnupiravir and even up tot 89% for nirmatrelvir/ritonavir, without evident safety concerns9-11.

The need for an independent Dutch cohort to evaluate the clinical use of new SARS-CoV-2 specific therapies
After the results of these first results of phase-III studies4,5, neutralizing monoclonal SARS-CoV-2 antibodies have been given an emergency use authorisation and - since late June 2021 - have become available in the Netherlands to treat SARS-CoV-2 infected patients who are at high risk to develop severe disease. Further randomized controlled trials investigating the effect SARS-CoV-2 antibody in immunocompromised patients are expected to be deemed unethical due to the clear effect seen in the phase-III trials and the already limited existing immune response. Of interest, there are currently intravenous and intramuscular antibodies treatment regimens available, although the shift to different routes, most notably subcutaneous, is underway and will possi

Study objective

This study has been transitioned to CTIS with ID 2024-515263-60-00 check the CTIS register for the current data.

- A. What are the SARS-CoV-2 viral load kinetics during and after treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?
- B. What is the risk of SARS-CoV-2 infection after prophylactic use of monoclonal antibodies or other antiviral agents?
- C. Do variants, spike mutations and immune escape during treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?
- D. What are the viral antibody and inflammatory response kinetics during and after treatment with neutralizing monoclonal antibodies and other antiviral agents against SARS-CoV-2?

Study design

The TURN-COVID biobank will be a prospective cohort study designed in accordance with international standards25. The study population will consist out of all patients treated with neutralizing monoclonal antibodies and antivirals against SARS-CoV-2. Clinical data will be obtained throughout the electronic patient dossier. In addition, control patients with similar comorbidities will be included.

In addition, patients with a high risk to develop severe Covid-19 and who are not treated with monoclonal antibodies or other antiviral agents against SARS-CoV-2 will be included as controls.
*
Scheme 1: SARS-CoV-2 infected patients treated with neutralizing monoclonal antibodies or/and other antiviral agents
Blood samples as detailed below will be sampled at day 0, 7, 28 and 90. Nasopharyngeal swabs will be sampled at day 0, 2, 5, 7, 28 and 90. The design is further visualized schematically in Figure 1. Patients will be asked to perform provided antigen-self test in the first 14 days of their SARS-CoV-2 infection. All self tests will be saved on room temperature for genetic characterization35.

Scheme 2: Patients treated with prophylactic neutralizing monoclonal antibodies or/and other antiviral agents
Blood samples and nasopharyngeal swabs as detailed below will be sampled at day 0, 28, 90, 180 and 360. In case patients experience symptoms that could indicate COVID-19 they are also asked to perform provided self-tests. A positive self test will be confirmed with an extra nasopharyngeal swab in order to perform a PCR. If a patient is infected with SARS-CoV-2 (= positive PCR) during the study period, they will also be included in Scheme 1 from the moment of confirmed SARS-CoV-2 infection. Patients will be asked to save their antigen test on room-temperature (self-tests), in order to perform genetic characterization and genomic surveillance for SARS-CoV-2.
The design is further visualized schematically in Figure 2. A three day deviation before and after the appointment is deemed acceptable for day 0, 2, 5 and day 7. For day 28 a seven day deviation is deemed acceptable, for day 90 and 180 a fourteen day deviation is deemed acceptable and for day 360 a twenty-eight day deviation is deemed acceptable. Samples will be stored in the Amsterdam UMC, location AMC.

Study burden and risks

Patients will be seen multiple times during follow-up. Venous blood and naso-oropharyngeal swabs will be obtained. The total burden and risk is deemed low.

Due to the fact that the METC classified this observational research as a medication study (non-registred) we also describe the risks associated with the monoclonal antibody and antiviral agents treatment, namely allergic reactions

and local reacties.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- All patients that are treated with neutralizing SARS-CoV-2 antibodies and other antivirals against or as prevention of SARS-CoV-2 as standard of care.
- Patients have to be aged >= 18 y.

Exclusion criteria

- No informed consent is provided by the patient

- Patients not suitable to fulfil study procedures

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2021
Enrollment:	1000
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evusheld
Generic name:	Tixagevimab/cilgavimab
Product type:	Medicine
Brand name:	Lagevrio
Generic name:	Molnupiravir
Product type:	Medicine
Brand name:	Paxlovid
Generic name:	nirmatrelvir + ritonavir
Product type:	Medicine
Brand name:	REGEN-COV2
Generic name:	casirivimab + imdevimab
Product type:	Medicine

Brand name:	Xevudy
Generic name:	Sotrovimab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-11-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-515263-60-00
EudraCT	EUCTR2021-005051-37-NL
CCMO	NL78705.018.21