An Open-Label Study Evaluating Anti-Viral Effects of Voclosporin in SARS-CoV-2 Positive Kidney Transplant Recipients - the VOCOVID Study

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Primary Objective: To investigate the kinetics of the anti-viral effects of VCS, compared to standard of care with TAC, on SARS-CoV-2 over 56 days, in stable KTRs.Secondary Objective: To assess the safety and tolerability of VCS in stable KTRs...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON55051

Source
ToetsingOnline

Brief title
the VOCOVID Study

Condition

- Viral infectious disorders
- Renal disorders (excl nephropathies)

Synonym
Coronavirus, COVID-19, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Aurinia Pharmaceuticals Inc.,Unrestricted grant van Aurinia Pharmaceuticals Inc.

Intervention

Keyword: Calcineurininhibitors, COVID-19, Transplantation, Voclosporin

Outcome measures

Primary outcome

The main endpoint is the time to viral clearance of SARS-CoV-2 , as measured by

first negative reverse transcription quantitative polymerase chain reaction

(RT-qPCR) with a CT value of >37 over 56 days.

Secondary outcome

The study will also assess predefined endpoints as surrogate markers of

(improved) viral clearance:

• Time to 2 consecutive negative RT-qPCR tests defined as a CT-value above 37

• Time to reduction in viral load below 3 log copies

• Time to 2 consecutive negative RT-qPCR tests defined as a CT-value above 24

• Time to clinical recovery, defined as free of symptoms for five days or more

• Time to clinical symptom relief, defined as free of symptoms for one day or

more

• Time to hospital discharge for hospitalized subjects

• Occurrence of treatment failures within the first 56 days, as defined by:

o Worsening of COVID infection requiring hospitalization for non-hospitalized

subjects

o Worsening of COVID infection for hospitalized subjects requiring admittance

to the intensive care unit (ICU) or death

• Safety and tolerability as assessed by adverse events (AEs), long-term effect

on graft function, incidence of rejection, formation of donor-specific

antibodies

Study description

Background summary

Calcineurin inhibitors (CNIs) are general immunosuppressive agents commonly used in the setting of transplantation to prevent solid organ rejection. CNIs form the cornerstone of immunosuppressive treatment in kidney transplant recipients (KTRs) including the 1st generation CNI Cyclosporin-A (CsA) and the most commonly employed 2nd generation CNI tacrolimus (TAC) (Hamawy, 2003). It is of interest that CNIs, especially CsA, also exert anti-viral effects in addition to immunosuppressive effects (Ma-Lauer et al, 2017 2016; Ishii et al, 2006; Qing et al, 2009; Braaten et al, 1996; Dang et al, 2017; de Wilde et al, 2011). Common side effects of CNIs are hypertension, new-onset diabetes, renal insufficiency and neurotoxicity. Therefore, in the recent decennium, efforts have been directed at developing a novel CNI, voclosporin (VCS), that has improved pharmacodynamic (PD) and pharmacokinetic (PK) attributes with respect to calcineurin inhibition as well as an improved safety profile to common side effects (Papp et al, 2008; Mayo et al, 2014; Kuglstatter et al, 2011). VCS has been extensively studied in KTRs demonstrating equivalent efficacy to TAC with respect to prevention of rejection while showing a reduction in CNI-related toxicity (Busque et al, 2011). Most recently, VCS as a component of multitargeted therapy demonstrated superior efficacy compared to standard of care in lupus nephritis (LN) patients (Rovin et al, 2018; Teng et al, 2020).

In 2011, a pivotal study from Leiden University Medical Center (LUMC) demonstrated in vitro anti-viral effect of CsA on Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) (de Wilde et al, 2011). Subsequently, VCS has been shown to have a more potent anti-viral effect on norovirus compared to CsA (Dang et al, 2017). The anti-viral effects of CNIs have a different mechanism of inhibition in each virus but mainly through inhibiting cyclophilins, an essential protein for viral replication. The SARS-CoV-1 interacts with human cyclophilins, however the role of these proteins in infection remains elusive (Wilde et al., 2018). Different reports stablished interactions between nsp1 (Pfefferle et al., 2011) or nucleocapsid (Luo et al., 2004; Chen et al., 2005) proteins with Cyps and hypothesize its influence in viral replication and viral entry. Unlike VCS and CsA, TAC binds to FK binding

proteins rather than cyclophilin A (CypA). Given the current COVID-19 pandemic, the LUMC has very recently demonstrated anti-viral effects of CNIs on SARS-CoV-2 infected cells in vitro: a 2-log reduction of SARS-CoV-2 viral titers in Calu-3 2B4 bronchial cell cultures (Tseng et al., 2005; Yoshikawa et al., 2010) was observed when incubated with ~3 µM VCS compared to 25µM CsA and 25µM TAC. In each experiment Remdesivir was taken as positive control as it inhibits viral replication by >4log at 10 µM concentration (Pruijssers et al., 2020). As such, VCS becomes an attractive and potentially feasible CNI to use or switch to in COVID-19 infected KTRs who are already using CNIs as part of their chronic immunosuppressive therapy.

Study objective

Primary Objective: To investigate the kinetics of the anti-viral effects of VCS, compared to standard of care with TAC, on SARS-CoV-2 over 56 days, in stable KTRs.
Secondary Objective: To assess the safety and tolerability of VCS in stable KTRs infected with SARS-CoV-2.

Study design

Open-label, 56 day, single-center, exploratory, proof-of-concept study of VCS with an extended safety follow-up, up to 1 year.

Intervention

At study entry, subjects are on standard therapy of dual immunosuppressive treatment of prednisone and TAC, as per current local guidelines (LUMC Transplant Center treatment guidelines for COVID-positive transplant patients). Following randomization, 10 out of 20 subjects will remain on this therapy for the duration of the study, while the other 10 subjects will switch to VCS (instead of TAC).

Study burden and risks

Because subjects will be randomized to either VCS or TAC as immunosuppressive agent during COVID-19 infection, the burden of the study is two-fold: first, subjects will need to switch to a novel CNI which intrinsically will harbour an uncertainty. However, from a clinical point-of-view VCS is proven equivalent to TAC with respect to organ rejection and safety monitoring of adequate drug levels is incorporated in the study. Secondly, subjects will need to agree to self assessments including monitoring of vital signs and collection of saliva samples and a throat swab in the first 56 days. We believe that it is actually in the interest of subjects to undergo this intensive monitoring because current standard practice is for KTRs with mild symptoms to not be hospitalized and stay at home until recovery without further monitoring. In addition, blood

sampling (10 x 38.5 mL), urine sampling and additional hospital visits will take place which are outside of normal clinical practice.
The potential advantage of the study to KTRs is that VCS may lead to a quicker reduction of SARS-CoV-2 viral load and quicker relief of symptoms. Altogether, we believe the burden of the study is minimal and outweighed by the potential benefit of the treatment on COVID-19 infection.

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

Subjects with a stable kidney transplant taking Tacrolimus and a confirmed diagnosis of SARS-CoV-2 with mild-to-moderate symptoms

Exclusion criteria

Severe symptoms resulting from SARS-CoV-2 infection requiring positive pressure ventilation at baseline

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-11-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orelvo
Generic name:	Voclosporin
Product type:	Medicine
Brand name:	Prograf
Generic name:	Tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-04-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-10-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EudraCT	EUCTR2020-001467-82-NL
CCMO	NL73762.058.20