WHO Collaborating Center on strongyloidiasis and other Neglected Tropical Diseases

IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore – Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato – Regione Veneto
DIPARTIMENTO DI MALATTIE INFETTIVE - TROPICALI E MICROBIOLOGIA
Direttore: Prof. Zeno Bisoffi

PROJECT PROPOSAL

TITLE: COVER study (COVid ivERmectin): a randomized, double-blind, multi-centre clinical trial on ivermectin for the early treatment of COVID-19
COORDINATING CENTRE: IRCCS Sacro Cuore Hospital, Department of Infectious – Tropical Diseases and Microbiology
DESCRIPTION OF THE COORDINATING CENTRE: The IRCCS Sacro Cuore Hospital is a main referral centre for infectious and tropical diseases in Northern Italy. The hospital has 508 beds for inpatients, 12 operating rooms plus 3 for day-surgery, an Intensive Care Unit with 12 beds. In 2018, the hospital has been appointed by the Italian Ministry of Health as Institute for Treatment and Research ("IRCCS") for tropical and infectious diseases in light of the patient care and research activities conducted by one of its departments, our Department of Infectious - Tropical Diseases and Microbiology (DITM). The latter includes the tropical and infectious diseases inpatients and outpatient clinics, and the Service of Epidemiology and Laboratory for Tropical Diseases. The DITM has extensive experience in diagnosis and treatment of tropical and infectious diseases. The molecular biology laboratory is equipped with cutting-edge instruments and the team gathers technicians and biologists with well-recognized experience in the set-up and validation of novel molecular biology diagnostic methods. The DITM is the referral centre for tropical and parasitic diseases of Veneto Region. Moreover, the DITM also coordinates the surveillance of arbovirus infections in Veneto Region since more than 10 years. Since September 2014, the DITM is also a WHO - collaborating centre on strongyloidiasis and other neglected tropical diseases. As such, it cooperates with tropical countries in research activities and implementation of WHO recommendations for novel control programmes for strongyloidiasis and laboratory follow up of neglected tropical diseases in endemic and non - endemic areas. Since 1996, the DITM has been involved in training programmes on tropical medicine and residential courses on diagnostics in the tropics. The Centre is also part of other European and International networks such as Tropnet (an European Network of more than 70 Institutions working on imported infectious and tropical diseases) and GeoSentinel (operative network of the International Society of Travel Medicine). Since last year, the DITM is coordinating the TropNet. Italy was one of the countries most hit by Covid-19, and hundreds of infected patients were diagnosed and admitted in our hospital. Our Institution participates to ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) in terms of reporting and sharing clinical and laboratory data on patients admitted with Covid-19. Moreover, research projects specifically related to Covid-19 were included in our research lines. Our Institution has participated and also coordinated randomized clinical trials, both for Covid-19 and other infections. Also, the DITM participated/coordinated population-based surveys or

Tel. 045 6013324
e-mail segreteria@malattietropicali.it
www.tropicalmed.eu

case-control studies aiming at estimating the prevalence of specific infectious diseases in the general population and/or in different cohorts of individuals. In the context of Covid-19, DITM participated to a population –based survey in Verona province, aiming at estimating the prevalence of the disease in the area. Prevalence surveys have been also been implemented in tropical countries, mainly in the context of the WHO-collaborating centre activities.

AIMS AND SCIENTIFIC PLAN:

Recently ivermectin, one of the most widely used medicines in tropical area, whose discovery resulted in the Nobel Prize for Medicine in 2015, has been proven effective in vitro in reducing the viral load of SARS-CoV 2 infected Vero cells (Caly et al. 2020). Ivermectin is an "old drug" (Omura 2008) extensively used on hundred millions people for over 35 years for a wide range of parasitic infections, and with a broadening range of potential indications in recent years.

Caly et al. hypothesized that the antiviral action against the SARS-CoV-2 in vitro was through the inhibition of the IMPα/β1 heterodimer-mediated nuclear import of viral proteins. However, the IC-50 for this antiviral effect was approximately 2.5 µM, equivalent to 2,190 ng/mL, that is about 50-fold higher than the peak concentration (Cmax) achieved in plasma after the single dose of 200 µg/kg, normally used as anti-parasitic drug in clinical practice (Muñoz et al. 2018; Buonfrate et al. 2019; Naquira et al. 1989).

This difference raised concern on the likelihood of a successful use of ivermectin for the treatment of COVID-19 (Chaccour et al. 2020), even using doses 10-fold higher than the approved one (Schmith et al., 2020).

However, the following points suggest that five daily doses of 600 and 1200 µg/kg in a fasted state, i.e. the schedule envisaged in the present CT, might allow to reach clinically relevant drug concentrations at the target organ (lung).

Antiviral drugs can probably play a role in the first phase of the infection as it has been demonstrated for remdesivir (but not for other antiviral medicines like lopinavir), by reducing the viral load before clinical complications arise. A viral load reduction is a pre-requisite for a possible clinical effect.

Primary objectives of the project:

The project is aimed:

1) at defining if ivermectin, administered at dosage of 600 µg/kg or 1200 µg/kg QD for five consecutive days, is safe in patients with initial, asymptomatic or oligosymptomatic SARS_CoV-2 infection,

2) at defining if ivermectin, administered at the dosage(s) found to be safe, decreases the viral load of SARS-CoV-2 at Day 7.

Secondary objectives

To assess

1. the temporal profile of viral load at baseline, day 7, 14 and 30
2. the time to clinical cure (for symptomatic patients)
3. the proportion of patients with virological clearance at day 14 and 30.
4. the hospitalization rate.

IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore – Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato – Regione Veneto
DIPARTIMENTO DI MALATTIE INFETTIVE - TROPICALI E MICROBIOLOGIA
Direttore: Prof. Zeno Bisoffi

5. the COVID-19 Severity Score at day 14 and 30

To reach the study objectives we estimated the need of a sample size of at least 60 patients (for the safety analysis), up to 130 patients (for the efficacy analysis).

STUDY BENEFITS AND EXPECTED OUTCOMES:

Expected results are that ivermectin is safe also at planned "antiviral" dosages in adults and efficacious in significantly reducing the SARS-CoV-2 viral load and consequently minimizing the risk of hospitalization and complications of COVID-19.

In case of positive results, ivermectin could be recommended (also in low-income countries) as part of the therapeutic strategy for COVID-19.

ESTIMATED BUDGET

The study has been already registered in clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04438850) and has received ethical clearance by the competent Ethical Committees. The only sponsor of the project is the IRCCS Sacro Cuore Hospital and investigators of the DITM already began with enrollement of the first patients. Therefor we are ready to conduct the project in real time.

The rapid evolution of COVID-19 pandemic and the concerning epidemiological curves, together with the disappointing lack of therapeutic weapons, calls for an acceleration of the enrolment process in order to reach as soon as possible relevant results.

In this way, a budget of 35000 euros could cover the expenses planned for personnel, patient follow-up and testing.

We can provide a detailed budget if requested.

Contact person:
Dr Andrea Angheben, MD
andrea.angheben@sacrocuore.it

Dr. Dora Buonfrate, MD, DTM&H
dora.buonfrate@sacrocuore.it

Prof. Zeno Bisoffi. MD, DTM&H, PhD
zeno.bisoffi@sacrocuore.it