Therapeutic plasma exchange followed by convalescent plasma transfusion in severe and critically ill COVID-19 patients: A single centre non-randomized controlled trial

trial registration number: NCT04973488 Date: 3 August, 2020

Study design, setting and population

A total of 38 Caucasian patients will be included in the present single center non-randomized controlled trial. All patients included in the study will be adults (>18 years) who present with acute respiratory failure and ARDS, and have positive reverse transcriptase-polymerase chain reaction (RT-PCR) test results for SARS-CoV-2 virus upon hospital admission. ARDS is defined as acute-onset hypoxemia (P/F ratio <300) with >50% bilateral pulmonary opacities on chest imaging within 24-48 h that are not fully explained by congestive heart failure and that require ICU treatment and monitoring. Exclusion criteria are represented by any of the following: Pregnancy, patients with suspected or confirmed pulmonary embolisms and patients with terminal disease, patients < 18 years of age. Patients enrolled in the study will be divided equally, non-randomized, into two groups as follows: A treatment group who will benefit of sequential TPE and CVP transfusion in addition to the standard treatment for COVID-19, and a control group who benefit of only standard treatment for COVID-19 (antiretrovirals, corticosteroids, anticoagulants and antibiotics if deemed necessary) according to hospital protocols.
All patients will provide written informed consent immediately after admission into the ICU regarding all the procedures performed during hospitalization, including the treatment scheme applied in the present study and the use of the resulting data in scientific research publications, with the assurance that they will remain anonymous. In cases where obtaining informed consent from the patients will not be possible due to their critical medical condition, a legal representative will be informed and provide written consent. The trial was approved by the Ethics Committee of 'Pius Brinzeu' Emergency Clinical County Hospital Timisoara (approval no. 91/03.08.2020).

Study protocol

The blood type of the patients will be determined immediately upon being admitted to the ICU. In the treatment group, a dual lumen, 14 French, dialysis catheter will be used for vascular access, by placing it in the femoral vein under echographic guidance. A single TPE session will be performed on the Infomed HF 440 machine (Infomed SA), with a plasma/blood separation ratio of 20%, using 40 ml/kg fresh frozen plasma as the substitute. The circuit will be anticoagulated with unfractioned heparin during the procedure. Upon completion of the TPE session, each patient from the treatment group will be transfused with 500 ml of ABO compatible CVP. Patients will be carefully monitored

during both the TPE session and the CVP transfusion, and also after the procedures, in order to treat emerging complications.

Patients from the treatment and control groups will receive standard treatment for COVID-19 according to hospital protocols, consisting of corticosteroids, antiretrovirals, anticoagulants and antibiotics if deemed necessary. Patients from both groups will be anticoagulated with subcutaneous nadroparine (Fraxiparine; Aspen Pharma Trading) in therapeutic dosage, once every 12 h, adjusted according to bodyweight (≤70 kg: 3,800 Anti-Xa IU; >70 kg: 5,700 Anti-Xa IU). Patients from the treatment and control groups will receive corticosteroids in the form of 16 mg dexamethasone (Dexamethason; Krka) divided into 2 doses, daily. Antiretrovirals administered will be the ones in the hosptital COVID-19 protocol lopinavir/ritonavir (Kaletra; Hetero Labs, Ltd.), 300 mg b.i.d. and remdesivir (Veklury; Gilead Sciences), 200 mg loading dose, then 100 mg o.d. for 5 days. Antimalarial drugs will also be used, in the form of hydroxychloroquine (Plaquenil; Sanofi-Aventis), 400 mg b.i.d. loading dose, then 200 mg b.i.d. Upon clinical (fever, chills, sweats or aspect/quantity of bronchial secretions) and paraclinical (leucocytosis, CRP or cultures) findings of infection, empiric antibiotics will be started, until de-escalation following culture results will be possible. Patients will be intensively monitored, and daily clinical and laboratory data will be collected during the ICU stay. Outcomes monitored will be survival at 30 days, oxygenation (P/F ratio) (normal ratio >300) and inflammatory markers [CRP (normal range 0-5 mg/l), LDH (normal range 135-225 U/l) and ferritin (normal range 30-400 µg/l)] at the 7-day follow-up, as assessed using ASTRUP analyses and blood tests.

Statistical analysis plan

Statistical data will be analysed using GraphPad Prism 8 (GraphPad Software, Inc.) and IBM SPSS Statistics 20 (IBM Corp.). The category variables will be characterized by value and percentage. Continuous variables will be presented as mean (± standard deviation) and median (interquartile range). Data distribution testing will be performed using the Shapiro-Wilk test. The numerical variables will be compared with the t-test for independent samples or the Mann-Whitney U test, depending on the type of distribution of the variables. The χ^2 test (or Fisher's exact test) will be used for the nominal variables. The Kaplan-Meyer method with the log-rank (Mantel-Cox) test will be applied to evaluate the primary endpoint. Cox regression will be utilized to determine hazard ratio of the treatment group. All statistical tests will be calculated with 2 tails and $P<0.05$ will be considered to indicate a statistically significant difference.

Local Ethics Committee Decision regarding Scientific Research in Human Subjects

SPITALUL CLINIC JUDEŢEAN DE URGENŢĂ „PIUS BRÎNZEU" TIMIŞOARA

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91/03.08. 2020

DECIZIA COMISIEI LOCALE DE ETICA PENTRU CERCETARE STIINTIFICA A SPITALULUI CLINIC JUDETEAN DE URGENTA TIMISOARA

Va comunicam avizarea din punct de vedere etic a studiului clinic cu titlul:

" Therapeutic plasma exchange succeeded by convalescent plasma transfusion in critically ill Covid -19 patients - a single center non- randomized controlled trial"

Departamentul in care se desfasoara: Compartiment ATI – Covid, Spitalul Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara, Sectia ATI Covid, Spitalul Clinic Municipal Lugoj

Persoane responsabile pentru desfasurarea studiului clinic: Conducator de doctorat- Prof. Dr. Licker Monica, Laborator Clinic Central, doctorand- dr. Novacescu Alexandru Noris, Clinica ATI - Spitalul Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara.

Studiul se va realiza in baza consimtamantului informat semnat de catre pacient/ reprezentant autorizat al pacientului la internarea in spital, consimtamant care cuprinde si investigatiile imagistice care se efectueaza pe perioada internarii. Se va asigura anonimizarea totala a investigatiilor, pentru a nu permite sub nici o forma identificarea pacientilor.

Componenta Comisiei Locale de Etica pentru Cercetare Stiintifica a Spitalului Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara este urmatoarea: Conf. univ. dr. Ovidiu Bedreag – membru, Asist. univ. dr. Razvan Bardan – membru, Prof. Dr. Mihaela Simu – membru.

Comisia Locala de Etica pentru cercetare Stiintifica a Spitalului Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara functioneaza in conformitate cu prevederile art 167 din Legea nr. 95/2006, art. 28, cap VIII din ordinul 904/2006 si cu EU GCP Directives 2005/28/EC, International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) si Declaration of Helsinki – Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects.

Coordonator Departament Cercetare Dezvoltare

Conf. dr. Ovidiu Bedreag