Official title

RESCUE Study
(Real-time Evaluation of Safety and efficacy of Convalescent plasma Units transfused to Elderly patients with COVID-19)

Brief title

Convalescent Plasma in COVID-19 Elderly Patients (RESCUE)

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Background

The trend of the spread of the CoVid-19 pandemic demonstrates in Lombardy, starting from 28.03.2020, a slowdown in the exponential phase of infections and the probable reaching of a plateau phase.

However, a marked increase in infections was observed in the so-called “protected structures" such as nursing homes (RSA), both in health staff and in the residents of such facilities. The observed percentage of lethality, according to the more recent data provided by the National Institute of Health, is very high especially among residents.

An immediate explanation of this phenomenon concerns the particular typology of these patients (frail patients of very old age, presence of one or more previous pathologies, possible promiscuity). This situation, particularly evident in the RSA of Lombardy, due to the greater spread of the virus in this region than in others, has created and is creating a real health and social emergency.

As suggested by the World Health Organization (WHO) itself, it is clear that the solution of this problem cannot be represented by the hospitalization of these fragile patients. This is true for three reasons: difficulty in transport and hospitalization in a hospital (due to prolonged bed rest, risk of co-infections etc.), risk of worsening the clinical condition of patients (COVID-19 related or not) and possible saturation of the same hospital structures, given the expected number of these cases.

Finally, the care of elderly patients with COVID-19 directly in RSAs aims to reduce the spread of the virus.

It is therefore evident that on-site management, with the possibility of carrying out medical checks, is the most suitable and practicable solution. These considerations appear in agreement with what recently suggested by the Lombardy Region itself, through the creation of the so-called Continuity Care Special Unit (USCA), which highlight the importance of managing the pandemic inside but also outside the hospital.

For these reasons, the Azienda Socio-Sanitaria Territoriale (ASST) of Mantua, already involved in the use of hyperimmune plasma as a therapy for COVID-19, designed this study in order to evaluate RSA patients and to identify the cases eligible for this treatment.

Study aims

The primary aim of this study is to evaluate the efficacy and safety of convalescent plasma in elderly patient with certain or probable COVID-19 infection, in order to cure the disease, avoiding patients aggravation and hospitalization.

Secondary aims are:

- the epidemiological evaluation of the spread of the virus in the RSA under study over time, expressed as the number of subjects with positive / total swab assisted, and trend in response to plasma therapy.

- To evaluate changes in sex hormones after convalescent plasma infusion (both in men and in women);

Study protocol

A medical team from the ASST of Mantua will perform clinical evaluations for patients admitted to the RSAs involved in this study. Practically, physicians experienced in thoracic ultrasound (Pneumology and Infectious Diseases specialists), will perform evaluation in RSAs to identify potential infected patients. These clinical evaluations will be mainly performed in patients with recent onset of COVID-19 -related symptoms and in patients with confirmed infection (according to the criteria reported in Attachment A). All enrolled patients will undergo thoracic ultrasound, biochemical exams and electrocardiogram (attachment A). These procedures will be carried out directly by the RSA staff according to this protocol.

Involved centres are located in Mantua and its province but the ASST of Mantua is willing to collaborate with RSAs of other provinces guaranteeing the supply of convalescent plasma (after the approval by local ethics committees). In addition, the number of RSAs involved in this project is related to the availability of convalescent plasma at the transfusion centre of Mantua Hospital.

Convalescent plasma is produced, processed and stored in agreement with the regulations in force on the subject and with the recent indications of the Italian National Blood Center (CNS). Convalescent plasma units with neutralizing titers equal to or greater than 1:40 will be used. The transfusion will be performed by the medical and nursing staff. All the procedures will be performed in agreement with the routine procedures of the Transfusion Service of Mantua.

Methods

The clinical assessments that will be performed are listed in Attachment A. Attachment A contains all the clinical, biochemical and instrumental data and will be used such as a Case Report Form (CRF). It will be filled in by the physician at each patient visit, i.e. on days +1, +3, +5 and +7.

All visits will be carried out by pneumologists of the ASST of Mantua.

A brief clinical history will be collected. A score was assigned to all clinical-instrumental tests; depending on the score achieved, patients will be classified as non-infected patients or patients with a low probability of contagion (score up to 4), with a high probability of infection and with confirmed infection. In patients with a score> = 5 the following tests will be performed: Pulse-OX, thoracic and abdominal ultrasound, ECG (if the patient has not done it previously) (attachment B).

Inclusion criteria:

- Elderly patients ($\geq$ 65 years old) with SARS-CoV-2 RT-PCR positivity on nasal swab or score higher than 5 with the following characteristics:

• New onset or worsening of recently onset respiratory symptoms (<10 days);

• Radiological imaging (CT, X-ray, Ultrasound) of bilateral pulmonary opacities not fully explained by pleural effusion, pulmonary or lobar atelectasis, pulmonary nodules;

• Respiratory failure (SpO2 <95%) not fully explained by heart failure or water overload (after excluding hydrostatic causes of edema in the absence of risk factors by objective assessment, for example ultrasound);

- Patients who have signed informed consent.

Exclusion criteria

- New onset or worsening of respiratory symptoms that began more than 10 days ago;

-Patients with proven hypersensitivity or allergic reaction to plasma, blood products or immunoglobulins;

- Manifest desire not to be included in the research protocol.

Patients with the inclusion criteria will be enrolled in the protocol and will be subjected to the following biochemical exams: blood group (day 1), blood count (day 1 and day 3), nasopharyngeal swab tests, C Reactive Protein (CRP), lactic dehydrogenase (LDH), Interleukin 6 (IL6), ferritin, creatinine, D-Dimer, Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serology for SARS-Cov-2 (IgG DiaSorin), lymphocyte subpopulations. In addition, clinical and instrumental monitoring will be performed (thoracic ultrasound). The laboratory tests will be performed at the Central Laboratory of the ASST in Mantua. All clinical, instrumental and laboratory tests will be performed on days +1 (baseline), +3, +5, +7 and the results will be entered in the appropriate CRF (Attachment A). The expected duration of the study to complete the enrolment of the 120 patients is estimated at 3 months.

Collection of blood samples

In order to monitor the response to therapy, blood samples will be taken on days +1. +3, +5 and +7 (as indicated in the previous chapter). In addition, a blood sample, always taken with the same timing, will be sent to the Mass Spectrometry Laboratory - Endocrinology Unit (Prof. Linda Vignozzi, Dr. Giulia Rastrelli, Dr. Vincenza di Stasi - Director Prof. Mario Maggi) of the Careggi Hospital of Florence to evaluate changes in sex hormones after convalescent plasma infusion (specifically, testosterone, DHEAS, Δ4-androstenedione, 17OH- progesterone, dihydrotestosterone, 17β-estradiol and estrone levels will be measured).

Expected results

- Identification of patients with COVID-19 infection at an early stage and assessment of the clinical response to the convalescent plasma infusion;

- Evaluation of the diagnostic accuracy of the clinical and instrumental tests used.

-Evaluation of the incidence of the COVID-19 pandemic in the RSAs involved in the project and of the containment measures undertaken, with particular reference to convalescent plasma transfusion.

Sample size and statistical analysis

According to the regional data provided and published, considering a mortality of around 30% in this category of elderly patients, the sample size required to ensure a power exceeding 80% with a survival of 85%, is 120 subjects. Categorical variables will be described as scores and percentages, quantitative ones with mean and standard deviation (if normally distributed) or median and interquartile range (if not normally distributed).

Study monitoring

As requested, the CNS and the Regional Coordination Structure will be informed on the start of the collection activity and on the quantities of plasma units donated / validated.

Adverse event reporting

The recording of each adverse reaction is foreseen, in accordance with the GVP of EMA (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/goodpharmacovigilance-practices), both in donors of plasma and in recipient patients.

Such reactions will be recorded using the National Information System of Transfusion Services (SISTRA) related to haemovigilance.

Informed consent of donors/patients

Informed consent is provided for both plasma donors and recipient patients.

Data collection

Data recorded on paper CRF (attachment A) will be transferred on electronic CRF, in order to perform statistical analysis. Data collection will be carried out continuously (daily) for the duration of the study. The publication of the study in an international journal is also planned. Ownership of the data will be of the workgroup.

Conflict of interest

The investigators declare that there are no conflicts of interest in connection with this study.

Centres involved in the study

This is a multicentre study, open to all RSAs in the province of Mantua and other provinces.

The participation of an RSA external to the province of Mantua implies adherence to the study by the Transfusion Service and by the specific ASST and notification to its Local Ethics Committee.