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Title: Tocilizumab (RoActemra) as early treatment of patients affected by SARS-CoV2 infection with severe multifocal interstitial pneumonia

Background

Multifocal interstitial pneumonia represents the most common cause of admission in intensive care units and death in SARS-CoV2 infections. Although information about pathological and pathophysiological features of alveolar-interstitial damage is very limited, few available data, mostly collected on other coronavirus infections with similar clinical behaviour (SARS1, MERS), seem to indicate as primary pathogenic mechanism an intense "cytokine storm" with a consequent inflammatory infiltrate of pulmonary interstitium, macrophage activation, giant cells formation and subsequent extended alveolar damage[1,2,3].

Tocilizumab, IL-6 inhibitor, has proved effective, as well as in chronic inflammatory diseases like rheumatoid arthritis, also in diseases characterized by an intense systemic inflammatory activation (Horton arteritis, Adult Still disease, Multifocal Castelman disease, Macrophagic Activation Syndrome). Moreover, anecdotal case reports in course of publication from China and Italy, seem to show efficacy in rapid improvement in patients affected by SARS-CoV2 interstitial pneumonia[4]. In our opinion the most rational use of this treatment is in patients with severe and worsening multifocal interstitial pneumonia before the appearance of an irreversible lung injury.

Aims

- To stop pulmonary function deterioration and/or to obtain a significant improvement of clinical and possibly radiological parameters
- To prevent the need of nasotracheal intubation
- To reduce the infection-related mortality

Study design

Simon's Optimal Two-stages design for Phase II clinical trial.

In details, we will enroll a first consecutive series of 10 patients (see population). If one or more of them will be classified as responder (see outcomes) within +7days , a second series of 20 patients will be treated. This design prevents from the exposition of a large number of patients to a drug with a likelihood of efficacy ≤10% and, in the meanwhile avoiding the premature discard of a therapy with a potential success rate ≥30% (alpha 0.05, power 80%)

Population

Settings:

Ospedali Riuniti di Ancona

- Sub-intensive care unit (Internal Medicine)
- Department of Infectious Diseases
- Intensive Care Unit (Department of Emergency)

Ospedali Marche Nord

- Sub-intensive care unit (Department of Emergency)

- Pneumology

Inclusion Criteria

- SARS-CoV2 Infection diagnosed by rt-PCR
- CT-scan confirmed multifocal interstitial pneumonia
- Need of oxygen therapy to maintain SO2>93%
- Worsening of lung involvement, defined as (one of the following criteria):
    - Worsening of oxygen saturation >3 percentage points or >10%, with stable FiO2 in the last 24h
    - Need of increase FiO2 in order to maintain a stable SO2 or new onset need of mechanical ventilation in the last 24h
    - Increase in number and/or extension of pulmonary areas of consolidation

Exclusion Criteria

- Age <18 ys and >90 ys
- Severe heart failure
- Bacterial Infection
- Haematological neoplasm
- Neutrophil count below 1000/mcl
- Platelet count below 50000/mcl
- ALT> x5UNL
- Inability to give informed consent

Note: at baseline all patients will be tested for HBsAg and treated with tenofovir in case of positivity

Outcome

Patient will be defined as RESPONDER in case of (one of the following):

- no further worsening of respiratory function as defined above
- Improvement of oxygen saturation >3percentage points or>10%, with stable FiO2 or possibility to reduce FiO2 to maintain adequate saturation
- Withdrawal of mechanical ventilation
- Improvement of HR CT-scan of the lung, defined as reduction (>30%) in extension or number of parenchimal consolidations

Patient will be defined as NON RESPONDER in case of (one of following):

- No evidence of improvement or worsening of lung involvement
- Need of naso-tracheal intubation
- Death

Outcome assessment

Patients will be evaluated at baseline (time 0) and +24h, +72h, +7days from infusion

At points +24h, +72h and 7 d the following items will be assessed:

Hemodynamic and respiratory parameters (see CRF for details), haemoglobin level, neutrophil and platelet counts, ALT, IL-6 levels, arterial blood test, glycaemia, pro-calcitonin. Moreover, 7cc of serum will be collected and stored for further evaluation.

At time 7 days a second HR CT-scan of the lung will be performed. All the images will be evaluated by a dedicated radiologist blinded for sequence.

Therapy Administration

Tocilizumab will be administered as a single dose intravenous infusion of 8mg/kg (maximal dose 800 mg) over 90 minutes, after premedication with a single dose of Chlorphenamine?

If the patient was not yet under steroid therapy with at least 40mg/di 6MPDN, Urbason 40mg will be administered, before Tocilizumab infusion.

Expected advers events

After Tocilizumab administration the following adverse events may occur and they will be noted on the case report form matched by a full description:

1. Low absolute neutrophil count < 1000/mcl
2. Low platelet count <100000/mcl
3. Increased ALT > 3 upper limit of normal (mild) or > 5 (severe)
4. Bacterial infection
5. Herpes zoster
6. Infusion reaction (urticaria, rash)

Any other adverse event will be recorded on patient's documentation.

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[1] Tian S[1], Hu W[2], Niu L[1], Liu H[1], Xu H[3], Xiao SY[4]. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol. 2020 Feb 27. pii: S1556-0864(20)30132-5. doi: 10.1016/j.jtho.2020.02.010. [Epub ahead of print]

[2] Ashour HM[1,2], Elkhatib WF[3,4], Rahman MM[5], Elshabrawy HA[6]. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. Pathogens. 2020 Mar 4;9(3). pii: E186. doi: 10.3390/pathogens9030186

[3] Channappanavar R[1], Perlman S[2]. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017 Jul;39(5):529-539. doi: 10.1007/s00281-017-0629-x. Epub 2017 May 2.

[4] Zumla A et al., Reducing mortality from 2019-nCoV: host-directed therapies should be an option; Lancet February 22, 2020; Vol 395, ISSUE 10224, Pe35-e36