Tocilizumab for treatment of SARS CoV 2 pneumonia. Experience in a private Health Center facility in Buenos Aires City.

Dr. Flavio Rotryng, Dra.Vanina Pagotto, Dr. Francisco Allalla, Dra. Paola Brunetti, Dra. Carla Tornatore, Dra. Valeria Tudanca, Dra. Lucila Villar, Dr. Hector Ferraro, Dr. Alejandro Schejtman, Dr. Nazareno Galvalisi

Introduction

Since the initial description on December 31st 2019 in Wuhan City, Hubei province (China); of an acute respiratory disease caused by a new coronavirus (SARS CoV-2) [1] and its spread worldwide, multiple and different treatment approaches have been studied.

ARDS is the main mortality cause in COVID-19 participants, and massive liberation of proinflammatory cytokines may contribute to their poor outcome [2].

Among therapeutic interventions, use of systemic steroids showed clear reduction in mortality in hospitalized participants with Coronavirus disease (COVID-19) and oxygen requirement [3].

In 2021, RECOVERY study [4] showed that tocilizumab (TCZ) decreased 28 day mortality among over 4000 SARS CoV2 pneumonia participants that required oxygen support of any type and had a C-reactive protein (CRP) level above 75 mg/L.

Besides, the REMAP-CAP [5] database showed that tocilizumab decreased hospital mortality in 800 participants who had initiated high-flow nasal oxygen (HFNO) or more intensive respiratory support in the previous 24 hours.

Considering this studies that showed evidence for its use, National Institute of Health of the United States (NIH) [6] and Infectious Diseases Society of America (IDSA) [7] recommendations; we elaborate our own recommendation guidelines for the use of this drug in Sanatorio Finochietto (Anexa 1 and 2).

Argentinian Health Ministry published an evaluation report on TCZ in May 2021, that concludes it probably reduces death and invasive mechanical ventilation (IMV) requirements in severe COVID participants [8].

Objectives

To describe clinical and laboratory characteristics and outcome of adult participants receiving only standard of care (SOC) versus participants receiving SOC plus TCZ as treatment for severe or critical SARS CoV2 pneumonia.

Material and methods

We conducted a retrospective observational study of adult participants receiving only SOC (dexamethasone 8 mg or its equivalent plus oxygen, HNFO or eventual IMV) versus participants receiving SOC plus TCZ (8mg/kg as a single dose) as treatment for severe or critical SARS CoV2 pneumonia. The inclusion date will be the date of admission, and follow up will conclude at death or discharge (whichever occurs first).

Settings

Emergency Department, General Ward and Intensive Care Unit (ICU) at Sanatorio Finochietto in Buenos Aires City, Argentina. Sanatorio Finochietto is a third level health care facility that provides health care services in prevalent clinical and surgical pathologies. It has the formerly mentioned units; as well as a Maternity Ward and complementary

services (such as Laboratory, Radiology and Hemodynamics) and a total of 161 beds 30 of which are ICU beds.

Population

Adult participants 18 years old and older receiving SOC plus TCZ versus only SOC as treatment for severe or critical SARS CoV2 pneumonia in Sanatorio Finochietto, between March 1st and August 31st 2021.
Participants in the control group couldn't receive TCZ because they were out of therapeutic window or had secondary infections suspicion.
Exposure variable is TCZ yes/no.

Inclusion Criteria

- Participants 18 years and older at admission.
- Confirmed diagnosis of severe SARS CoV 2 infection.
- Participants in category 6 and 7 of World's Health Organization (WHO) COVID 19 ordinal scale on Clinical Improvement (in Annexa).

Variables of study

1) Sociodemographics:
    a) Sex. Categoric, dichotomous. M: male. F: female.
    b) Age. At time of admission. Numerical, continual, in years.
    c) Weight. At time of admission. Numerical, continual, in kg.
    d) Height. Numerical, continual, in cm.
    e) Body Mass Index (BMI). Numerical, continual. It will be calculated by the formula weight/height^2.
2) Clinical characteristics
    a) Medical History. Nominal category. 1: Asthma 2: Chronic Obstructive Pulmonary Disease (COPD) 3: Diabetes (DBT) 4: High blood pressure (HBP) 5: Obesity 6: Coronary disease 7: Heart failure 8: Solid Tumor 9: Oncohematologycal diseasse 10: Person living with Human Immunodeficiency Virus (PLWHIV).
    b) Acute Physiology and Chronic Health Evaluation II (APACHE II). Numerical, continual.
    c) Symptoms onset date. Numerical, continual.
    d) Admission date. Numerical, continual.
    e) Steroids onset date. Numerical, continual.
    f) Total steroids days. Numerical, continual. Defined as dexamethasone dose equal or over 8 mg.
    g) Methylprednisolone pulse. Nominal category. Yes/No. Defined as infusion of at least 500 mg methylprednisolone.
    h) Number of methylprednisolone pulses. Numerical, continual.
    i) IMV. Nominal category. Yes/No.
    j) IMV days. Numerical, continual.
    k) HNFO. Nominal category. Yes/No.
    l) HFNO. Numerical, continual.
    m) Shock. Nominal category. Yes/No. Defined as vasopressor requirements for 24 hours or more.

n) Other organ failure. Nominal category. Yes/No. Defined as organ failure besides hemodinamic or respiratory failure.
o) Worsening date. Numerical, continual. Worsening is defined as more oxygen requirement (non rebreather mask or high nasal flow oxygen).
p) TCZ infusion. Nominal category. Yes/no.
q) TCZ infusion date. Numerical, continual.
r) TCZ dose. Numerical, continual.
s) TCZ adverse reaction. Nominal category. Yes/No. Defined as adverse reaction during infusion, neutropenia at 24/48 hs and 7th day or discharge (whichever occurs first) and/or hepatic enzymes elevation above five times normal value at 24/48 hs and 7th day or discharge (whichever occurs first).
t) WHO COVID 19 ordinal scale on Clinical Improvement at worsening. Numerical, continual.
u) WHO COVID 19 ordinal scale on Clinical Improvement at 14th day or discharge (whichever occurs first). Numerical, continual.
v) CRP value. Numerical, continual. At tociluzumab's infusion date or closest previous.
w) Ferritin value. Numerical, continual. At tociluzumab's infusion date or closest previous.
x) D dimer value. Numerical, continual. At tociluzumab's infusion date or closest previous.
y) CRP value at discharge. Numerical, continual. At discharge or closest previous.
z) Ferritin value at discharge. Numerical, continual. At discharge or closest previous.
aa) D dimer value at discharge. Numerical, continual. At dishcarge or closest previous.
bb) Secondary infections. Open
cc) Survival. Nominal category. Yes/no.
dd) Cause of death. Open.
ee) Discharge date. Numerical, continual.

Data circuit

Information will be collected from electronic records.
Given that all severe SARS CoV 2 pneumonia participants with SOC or SOC plus TCZ will be included, sample calculation won't be estimated.

Statistical analysis

In the descriptive analysis, quantitative data are expressed as mean and standard deviation or median and interquartile range 25-75 (IQR) according to their distribution. Data normality was evaluated using charts and Kolmogorov-Smirnov's test. Qualitative data are expressed as absolute and relative frequency in percentage. For comparison between groups, chi2 or Fisher test were used according to assumptions for qualitative data and Wilcoxon for quantitative data according to their distribution. A significance level of less than 0.05 was considered. R software version 4.0.3 was used.

Ethical considerations

This investigation will be conducted under national and international regulatory rules about human health investigations; and according to Ministry Resolutions, Helsinki declaration and all its amendments and Good Clinical Practice Guidelines ICH E6.
All study data will be processed with the utmost confidentiality and anonymously, with restricted access only to authorized personnel and for study purposes only according to current legislation of National Personal Data Protection Laws (Ley de Habeas data) and Law 26529/09.
Data will be encoded using a numerical code randomly generated. This code will replace the patient's name and last name. Identificatory data in database comprehensed in the 18 identifiers of HIPPA rules will be eliminated (A su vez se eliminarán los datos identificatorios de la base de datos a analizar comprendido por los 18 identificadores detallados por las normas HIPAA). Database will be saved in a computer and accessed with a code and only by the principal investigator. After statistical analysis it will be eliminated.
This is an observational study and uses a secondary database, and constitutes a minimal risk investigation; so according to CIOMS 2016 and Pauta 10, exception of informed consent for participants is requested.

Endpoints

Secondary infections, death at discharge, WHO COVID 19 ordinal scale on Clinical Improvement at 14 days from worsening WHO COVID 19 ordinal scale on Clinical Improvement (whichever occurs first).

Financing

Cost in administrative and human resources for the study will be assumed by principal investigators. There will be no extraordinary costs for subjects nor health care providers.

Interest conflicts

Investigators declares none interest conflicts

Anexa

Annex 1

Indications for the use of Tocilizumab in participants with Covid (Sanatorio Finochietto's treatment committee)

1- Participants with a confirmed COVID diagnosis plus oxygen requirement (HFNO, IMV, NIVM). In such cases, CRP value over 75 could be added as additional criteria (not resolved).

2- Participants with a low flow oxygen requirement that presents rapidly progressive clinical and gasometric worsening despite steroid use.

Tocilizumab's proposed dose is 8 mg/kg (800 mg maximum) for one time only. This recommendation arises from lack of clear evidence that a second dose is better than a single dose (and if it increases costs substantially).

NOTE: participants should receive systemic steroids (e.g. dexamethasone) in all cases where tocilizumab is administered.

Comité de Tratamiento Sanatorio Finochietto

1- Pacientes con diagnóstico confirmado de COVID con requerimiento de 02 suplementario a través de CNAF, VNI o AVM. En estos casos podría sumarse el valor de PCR > de 75 como criterio adicional (punto no resuelto).

2- Pacientes con necesidad de 02 suplementario a bajo flujo que pese al uso de esteroides sistémicos presentan un rápido deterioro clínico y gasométrico asociado a PCR > de 75.

La dosis de tocilizumab propuesta es: 8 mg/k (máximo 800 mg/dosis) por única vez.

Esta recomendación surge de no haber evidencia clara respecto a que repetir una segunda dosis de Tocilizumab sea mejor que una sola (y si incrementa los costos de manera sustancial).

NOTA: En todos los casos donde se utilice tocilizumab, los pacientes deben recibir esteroides sistémicos (ej. dexametasona)

Annex 2

Recommendations for the use of Tocilizumab in participants in General Ward and Emergency Room of Sanatorio Finochietto. May 14th 2021

1- Hospitalized COVID participants with oxygen requirements.

2- On treatment with systemic steroids in the previous 24 hs (at least dexamethasone 8 mg every day or its equivalent).

3- Rapidly progresive worsening (requiring more than 5 lts/min oxygen flow by nasal cannula or non rebreather mask).

4- Plus one of the following: Increasing CRP or total value more than 75, 60 years or older, Diabetes, COPD, High blood pressure, Obesity, Inmunosupresion.

NOTES:

- Infusse ideally in the first 24 hs from worsening.
- All four points must be fulfilled. Exceptions may exist, and they should be discussed between the Emergency Department, Infectious Diseases and Internal Medicine.
- It should always be authorized by the Department´s chief or coordinators.

Recomendaciones para el uso de Tocilizumab en pacientes en Sala de Internación General y Servicio de Emergencias del Sanatorio Finochietto. 14 mayo 2021

1-Pacientes hospitalizados con neumonía COVID con requerimiento de 02.
2- Bajo tratamiento con esteroides sistémicos en las 24 hs previas. (al menos 8 MG/día de dexametasona o su equivalente)
3- Que progresa rápidamente (requiere cánula alto flujo a > de 5 lt/min de 02 o máscara reservorio)
4- Y alguno de los siguientes: PCR en ascenso o mayor a 75, Edad mayor a 60 años Diabetes, EPOC, HTA, Obesidad, inmunosupresión.
NOTAS:

- Administrarlo idealmente dentro de las 24 hs del empeoramiento respecto al basal.
- Deben cumplirse los 4 puntos mencionados para la administración de TCL aunque pueden considerarse excepciones (en casos que se generen dudas o controversias se discutirá interservicios: Emergencias, Infectología y Medicina Interna.
- Siempre con autorización de Coordinación o Jefatura de Servicio.

Annex 3

Definitions and abbreviations

- Standard of care: for participants with oxygen requirement, steroid use administered by mouth or intravenously at a dexamethasone dose of 8 mg (or its equivalents) plus oxygen administered by nasal cannula, non rebreather mask, HFNO or IMV.
- CRP: C reactive protein value at Tocilizumab infusion day or closer.
- DD: D dimer value at Tocilizumab infusion day or closer.
- Worsening: more oxygen requirement (more than 5 lts/min oxygen flow by nasal cannula or non rebreather mask, HFNO or IMV)
- Ferritin: ferritin value at Tocilizumab infusion day or closer
- Solid Tumor: active cancer
- Hematological disease: active hematological disease
- HIV: HIV infection
- Coronary heart disease: previous coronary heart disease diagnosis.
- Heart failure: previous heart failure diagnosis
- Obesity: BMI over 30
- BMI: Body Mass Index
- IMV: Invasive Mechanical Ventilation
- HNFO: High Nasal Flow Oxygen
- ECMO: Extracorporeal membrane oxygenation
- NIV: non invasive ventilation
- Organ failure: organ failure excluding respiratory failure and shock
- Shock: vasopressors requirement for over 24 hours
- Cause of death: active diagnosis at time of death

Annex 4
WHO COVID 19 ordinal scale on Clinical Improvement

Score	Description
8	Death
7	Hospitalized. On IMV or ECMO
6	Hospitalized. On NIV or high flow oxygen devices
5	Hospitalized. Low flow oxygen requirements.
4	Hospitalized. No oxygen requirements, but requires ongoing medical care
3	Hospitalized. No oxygen requirement, no ongoing medical care required
2	Ambulatory. Limitation of activities, home oxygen requirement or both
1	Ambulatory. No limitation of activities

Bibliography

1- Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China- Lancet. 2020 15-21 February; 395(10223): 497–506. Published online 2020 Jan 24. doi: 10.1016/S0140-6736(20)30183

2- P. Mehta, D.F. McAuley, M. Brown, *et al.* COVID–19: consider cytokine storm syndromes and immunosuppression Lancet, 395 (10229) (2020), p. 1033 –4)

3-Dexamethasone in Hospitalized Patients with Covid-19 The RECOVERY Collaborative Group* N engl j med 384;8 nejm.org February 25, 2021

4- Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial RECOVERY Collaborative Group. www.thelancet.com Vol 397 May 1, 2021

5- Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 The REMAP-CAP Investigators* N engl j med 384;16 nejm.org April 22, 2021

6- NIH COVID Treatment Guidelines: Interleukin-6 Inhibitors. Ultima actualización: April 21, 2021. https://www.covid19treatmentguidelines.nih.gov/immunomodulators/interleukin-6-inhibitors

7- IDSA Guidelines on the Treatment and Management of Patients with COVID-19 Published by IDSA on 11/04/2020. Ultima actualización: 14/04/2021 https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-m

8- ACTUALIZACIONES BASADAS EN EVIDENCIA COVID-19 Tocilizumab para el tratamiento de pacientes con COVID-19. https://www.argentina.gob.ar/sites/default/files/informe-covid-19-n6-tocilizumab.pdf (visitada 29/7/2021)