CNI & COVID19

Shahram Taheri MD.
Associate Prof., Internist/nephrologist
Isfahan Kidney Diseases Research Center
Isfahan University of Med. Sciences

Introduction

- In recent months, the coronavirus disease 2019 (COVID-19) pandemic has stressed healthcare systems worldwide and the World,
- Health Organization has declared it a global health emergency.
- Patients receiving immunosuppressive treatment, for example, due to organ transplantation or autoimmune disease, are instructed to isolate at home because of a presumed higher risk of more serious disease and possible death.

transplantology

MDPI

Review

Transplant Drugs against SARS, MERS and COVID-19

René Hage [1,2,*], Carolin Steinack [1,2], Fiorenza Gautschi [1,2] and Macé M. Schuurmans [1,2]

1 Division of Pulmonology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland; carolin.steinack@usz.ch (C.S.); fiorenza.gautschi@usz.ch (F.G.); mace.schuurmans@usz.ch (M.M.S.)
2 Faculty of Medicine, University of Zurich, Raemistrasse 71, 8006 Zurich, Switzerland
* Correspondence: rene.hage@usz.ch

Received: 14 August 2020; Accepted: 18 September 2020; Published: 3 October 2020

Abstract: There is an urgent need to develop drugs and vaccines to counteract the effects of the new coronavirus SARS-CoV-2 and adequately treat the corona virus disease (COVID-19). As these drugs are still under investigation, research also focuses on existing medication with proven effectiveness in other coronaviral diseases. The advantages of existing therapeutic drugs that are currently approved (for other indications) are the known safety profile, general availability and relatively lower costs involved in extending the purpose to a new disease. Calcineurin inhibitors (CNI) are drugs that have shown effectiveness in several coronaviral diseases, and are well-known and widely used drugs in transplant medicine. The aim of this narrative review is to present the current evidence of CNI in

Introduction

- Calcineurin inhibitors (CNI) are drugs that have shown effectiveness in several coronaviral diseases, and are well-known and widely used drugs in transplant medicine.
- The aim of this narrative review is to present the current evidence of CNI in coronaviral diseases, the biophysiology of CNI and to suggest possible ways to study CNI as a new treatment option for COVID-19.

Treatment of Coronaviruses

- There is an urgent need to develop therapeutic drugs and vaccines against SARS-CoV-2 for the treatment and prevention of COVID-19, respectively.
- As these drugs still are under investigation, research also focuses on existing drugs with proven effectiveness in other (corona-)viral diseases.
- Sometimes this is referred to as “repurposing”. Using currently approved drugs for other indications reduces time, costs and safety issues.

Treatment of Coronaviruses

- Calcineurin inhibitors (CNI) showing favorable effects in multiple coronaviruses, thereby replacing the “one-drug-for-one-bug” paradigm.
- They are well-known, already existing drugs in transplant medicine used for solid organ transplant (SOT) recipients, and are also prescribed in rheumatology, dermatology and ophthalmology.

Table 1. Coronaviral serotypes and treatment with calcineurin inhibitors.

Coronaviral Serotype Studies in Humans	CNI	Remarks	Ref. No.
MERS-CoV	Tac	renal transplant recipient on tacrolimus survived	[11]
MERS-CoV	CsA	inhibition of viral replication	[12]
Coronaviral Serotype Studies in Animals	**CNI**	**Remarks**	**Ref. No.**
feline CoV	CsA	inhibition of viral replication in dose-dependent manner	[13]
turkey CoV	CsA	enhanced virus titers in kidney	[14]
Coronaviral Serotype Studies In Vitro	**CNI**	**Remarks**	**Ref. No.**
MERS-CoV	CsA + IFN-α	inhibition of viral replication	[15]
MERS-CoV, SARS-CoV	ALV	inhibition of viral replication	[16]
SARS-CoV, CoV-229E	CsA	inhibition of viral replication SARS-CoV replication impaired, but not fully blocked (1–5% of cells remained SARS-CoV positive, even in high CsA concentrations)	[17]
CoV-NL63, CoV-229E, SARS-CoV	CsA	inhibition of viral replication	[18]
SARS-CoV, CoV-NL63, CoV-229E	Tac	inhibition of viral replication	[19]
CoV-NL63	CsA-d	inhibition of viral replication by CsA derivatives (Alisporivir, NIM811)	[19]
SARS-CoV-2	CsA	potent antiviral activity in SARS-CoV-2, cyclophillin depedent (and calcineurin independent)	[20]

ALV = alisporivir, CNI = calcineurin inhibitor, CoV = coronavirus, CsA = cyclosporin A, CsAd = cyclosporine A derivatives, IFN-α = interferon alpha, MERS = Middle East respiratory syndrome, Tac = tacrolimus.

microorganisms

MDPI

Communication

Calcineurin Inhibitor-Based Immunosuppression and COVID-19: Results from a Multidisciplinary Cohort of Patients in Northern Italy

Lorenzo Cavagna [1,*,†], Elena Seminari [2], Giovanni Zanframundo [1], Marilena Gregorini [3], Angela Di Matteo [2], Teresa Rampino [3], Carlomaurizio Montecucco [1], Stefano Pelenghi [4], Barbara Cattadori [4], Eleonora Francesca Pattonieri [3], Patrizio Vitulo [5], Alessandro Bertani [6], Gianluca Sambataro [7], Carlo Vancheri [7], Alessandro Biglia [1], Emanuele Bozzalla-Cassione [1], Valentina Bonetto [8], Maria Cristina Monti [9], Elena Ticozzelli [10], Annalisa Turco [11], Tiberio Oggionni [12], Angelo Corsico [12], Francesco Bertuccio [12], Valentina Zuccaro [2], Veronica Codullo [1], Monica Morosini [12], Carlo Marena [13], Massimiliano Gnecchi [14,15], Carlo Pellegrini [4] and Federica Meloni [12]

Received: 2 June 2020; Accepted: 28 June 2020; Published: 30 June 2020

Abstract: The role of immunosuppression in SARS-CoV-2-related disease (COVID-19) is a matter of debate. We here describe the course and the outcome of COVID-19 in a cohort of patients undergoing treatment with calcineurin inhibitors. In this monocentric cohort study, data were collected from the COVID-19 outbreak in Italy up to 28 April 2020. Patients were followed at our hospital for solid organ transplantation or systemic rheumatic disorders (RMDs) and were on calcineurin inhibitor (CNI)-based therapy. Selected patients were referred from the North of Italy. The aim of our study was to evaluate the clinical course of COVID-19 in this setting. We evaluated 385 consecutive patients (220 males, 57%; median age 61 years, IQR 48–69); 331 (86%) received solid organ transplantation and 54 (14%) had a RMD. CNIs were the only immunosuppressant administered in 47 patients (12%). We identified 14 (4%) COVID-19 patients, all transplanted, mainly presenting with fever (86%) and diarrhea (71%). Twelve patients were hospitalized and two of them died, both with severe comorbidities. No patients developed acute respiratory distress syndrome or infectious complications. The surviving 10 patients are now fully recovered. The clinical course of COVID-19 patients on CNIs is generally mild, and the risk of superinfection seems low.

COVID-19 infection in kidney transplant recipients

Debasish Banerjee[1,2], Joyce Popoola[1,2], Sapna Shah[3], Irina Chis Ster[4], Virginia Quan[5] and Mysore Phanish[5,6]

OPEN

By 21 March 2020 infections related to the novel coronavirus SARS-CoV-2 had affected people from 177 countries and caused 11,252 reported deaths worldwide. Little is known about risk, presentation and outcomes of SARS-CoV-2 (COVID-19) infection in kidney transplantation recipients, who may be at high-risk due to long-term immunosuppression, comorbidity and residual chronic kidney disease. Whilst COVID-19 is predominantly a respiratory disease, in severe cases it can cause kidney and multi-organ failure. It is unknown if immunocompromised hosts are at higher risk of more severe systemic disease. Therefore, we report on seven cases of COVID-19 in kidney transplant recipients (median age 54 (range 45-69), three females, from a cohort of 2082 managed transplant follow-up patients) over a six-week period in three south London hospitals. Two of 32 patients presented within

Table 1 | Clinical characteristics and outcome of 7 kidney transplant patients with COVID-19 infection

Patient	Age/sex	Tx date	Comorbidities	Respiratory and renal involvement	Baseline creatinine (eGFR ml/min per 1.73 m^2)	Baseline immunosuppression and treatment	ACEI or ARB	Outcome
1	48/M	1989	HT	No	350 (15–18)	Aza/Pred No change	No	Stayed at home, full recovery
2	67/F	03/2019	T2D/HT	Yes, ARDS + AKI (CVVH)	150 (45)	Tac/MMF/Pred MMF stopped	Yes ACEI	Died
3	54/F	12/2019	PTDM/CMV	Yes, ARDS + AKI (CVVH)	132 (48)	Tac/MMF/Pred Tac and MMF stopped	No	Alive, ventilated
4	65/M	08/2018	Wheelchair/ HTN	No ARDS	180 (23)	Tac/MMF/Pred MMF stopped	No	Alive, in medical ward
5	69/F	02/2020	DM/HT	No ARDS AKI	165 (31)	Tac/MMF/Pred MMF stopped	No	Brief ITU stay, not intubated; stepped down to ward
6	54/M	05/2013	Hemolytic anemia/HT	No ARDS	187 (47)	Tac/MMF MMF stopped	No	Stayed at home, still has cough and some flu-like symptoms
7	45/M	09/2017 (2nd Tx)	HT	No ARDS AKI (HD)	450 (12–16)	Tac/Aza/Aza Aza stopped Tac dose reduced	No	Admitted, managed in the ward; severe AKI

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; Aza, azathioprine; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CVVH, continuous venovenous hemofiltration; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; ITU, intensive therapy unit; M, male; MMF, mycophenolate mofetil; Pred, prednisolone; PTDM, posttransplant diabetes mellitus; T2D, type 2 diabetes; Tac, tacrolimus; Tx, treatment(s).

7 Studies found for: **calcineurin inhibitor | covid19**

Also searched for **COVID**. See Search Details

Your search included: **covid19**

Learn more about clinical studies related to COVID-19:

- **ClinicalTrials.gov**: Federally-funded clinical studies related to COVID-19
- **WHO Trial Registry Network**: COVID-19 studies from the ICTRP database
- **NIH**: COVID-19 Treatment Guidelines
- **ClinicalTrials.gov**: Views of Listed COVID-19 Studies (Beta)

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Corona Virus Infection Among Liver Transplant Recipients	• SARS-CoV Infection • Corona Virus Infection • Liver Transplant		• Assiut University Assiut, Egypt

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Corona Virus Infection Among Liver Transplant Recipients	• SARS-CoV Infection • Corona Virus Infection • Liver Transplant Recipient • **COVID-19**		• Assiut University Assiut, Egypt
2	☐	Recruiting	Cyclosporine in Patients With Moderate **COVID-19**	• **COVID-19**	• Drug: Cyclosporine	• University of Pennsylvania Philadelphia, Pennsylvania, United States
3	☐	Not yet recruiting	Cyclosporine A Plus Low-steroid Treatment in **COVID-19** Pneumonia	• **COVID 19** Pneumonia	• Drug: Cyclosporin A	• Jose Luis Jl Galvez-Romero Puebla, Mexico
4	☐	Recruiting	Clinical Trial to Assess Efficacy of cYclosporine Plus Standard of Care in Hospitalized Patients With **COVID19**	• **COVID19** Infection	• Drug: Cyclosporine • Drug: Standard treatment	• Complejo Hospitalario Universitario La Coruña La Coruña, Galicia, Spain • Hospital Quiron La Coruña La Coruña, Galicia, Spain • Hospital Rey Juan Carlos Mostoles, Madrid, Spain • (and 4 more...)
5	☑	Recruiting	Clinical Trial to Evaluate Methylprednisolone Pulses and Tacrolimus in Patients With **COVID-19** Lung Injury	• **COVID-19** • Lung Injury	• Drug: Tacrolimus • Drug: Methylprednisolone	• Hospital Universitari de Bellvitge L'Hospitalet de Llobregat, Barcelona, Spain
6	☐	Recruiting	Cyclosporine For The Treatment Of **COVID-19**(+)	• SARS (Disease)	• Drug: Cyclosporine • Other: Standard of Care Treatment	• Baylor College of Medicine Houston, Texas, United States
7	☐	Not yet recruiting	Topical Steroids and Cyclosporin-A for **COVID-19** Keratoconjunctivitis	• Keratonjunctivitis	• Drug: topical steroids and cyclosporin-A	• Farawanyia hospital Kuwait, Farawanyia, Kuwait

Trial record **2 of 7** for: calcineurin inhibitor | covid19

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Cyclosporine in Patients With Moderate COVID-19

ClinicalTrials.gov Identifier: NCT04412785

Recruitment Status : Recruiting
First Posted : June 2, 2020
Last Update Posted : October 23, 2020

See Contacts and Locations

Sponsor:
University of Pennsylvania

Information provided by (Responsible Party):
University of Pennsylvania

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Study Description

Go to

Brief Summary:

Phase 1 safety study to determine the tolerability, clinical effects, and changes in laboratory parameters of short course oral or IV cyclosporine (CSA) administration in patients with COVID-19 disease requiring oxygen supplementation but not requiring ventilator support.

Condition or disease	Intervention/treatment	Phase
COVID-19	Drug: Cyclosporine	Phase 1

Detailed Description:

Our overall hypothesis is that CSA is safe in this patient population and that it will have antiviral and anti-cytokine effects as measured in laboratory tests.

The initial dose will be 9 mg/kg/day oral divided q12h or 3 mg/kg/day by continuous IV infusion. Oral administration is generally preferred, however IV administration can be used if oral administration is not feasible or cannot be tolerated, or at the physician-investigator's clinical discretion. The dose will be adjusted to target a trough level of 200 to 300 ng/ml, which is in alignment with common clinical practice. The planned duration of CSA treatment is up to 14 days, with planned discontinuation upon discharge from the hospital. Dose reduction of 25% to 50% can be made for patients who experience adverse events such as hypertension or serum creatinine elevation.

The end of study will be study day 30 for those patients who have been discharged from the hospital. If the patient remains in the hospital, the subject will still complete the end of study visit at day 30 as planned, but will continue to be followed until date of discharge.

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	20 participants
Allocation:	N/A
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Phase I Trial for the Prevention of Cytokine Release Syndrome (CRS) With Cyclosporine in Patients With Moderate **COVID-19**
Actual Study Start Date :	June 30, 2020
Estimated Primary Completion Date :	April 2021

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Single Arm Cyclosporine; oral or IV route of administration, per investigator discretion. Duration of administration up to 14 days, as tolerated.	Drug: Cyclosporine • The initial dose will be 9 mg/kg/day oral divided q12h. For IV, the dose will be 3mg/kg/day by continuous IV infusion. Other Name: Sandimmune, Neoral, Gengraf

Outcome Measures

Go to

Primary Outcome Measures :

1. Safety-oxygen, ICU transfer and ventilation [Time Frame: 3 months]

   Safety will be measured: By assessing the proportion of participants requiring increase in oxygen requirements, transfer to intensive care unit, and/or mechanical ventilation

2. Safety-changes in absolute lymphocyte count [Time Frame: 3 months]

   Safety will be assessed: By monitoring changes in absolute lymphocyte counts

3. Safety-changes in creatinine clearance [Time Frame: 3 months]

   Safety will be assessed: By monitoring changes in creatinine clearance. Creatinine clearance will be estimated using the Cockcroft-Gault formula.

4. Safety-secondary bacterial infections [Time Frame: 3 months]

   Safety will be assessed: By monitoring the incidence of secondary bacterial infections complicating COVID-19 hospitalization

Secondary Outcome Measures :

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged >18.
4. Admitted to hospital with laboratory confirmation of SARS-CoV-2 infection.
5. Estimated creatinine clearance >50 ml/min using standard Cockcroft-Gault formula.

Exclusion Criteria:

1. Are admitted to the ICU at time of enrollment.
2. Have an active uncontrolled infection with a non-COVID-19 agent.
3. Have an active malignancy, not including non-melanoma skin cancer, superficial cervical or bladder cancer, MGUS, or prostate cancer with PSA <1.0.
4. Are on chronic immune suppressive medications, including
5. corticosteroid therapy at a prednisone equivalent dose of 10 mg per day or higher; therapy with calcineurin inhibitors or mTOR inhibitors.
6. Are pregnant
7. Are lactating
8. Have a known allergic reaction to components of the CSA or its diluents.
9. Are receiving investigational vaccine for SARS-CoV-2.

Contacts and Locations

Go to

Cyclosporine For The Treatment Of COVID-19(+)

ClinicalTrials.gov Identifier: NCT04492891

Recruitment Status : Recruiting
First Posted : July 30, 2020
Last Update Posted : November 27, 2020

See Contacts and Locations

Sponsor:
Bryan Burt, MD

Collaborator:
Brigham and Women's Hospital

Information provided by (Responsible Party):
Bryan Burt, MD, Baylor College of Medicine

Study Description

Go to

Brief Summary:

Phase IIa clinical trial in which 75 non-ICU hospital inpatients will be randomized 2:1 to 7 days of an oral formulation of cyclosporine, Neoral (2.5mg/kg PO BID) + standard of care (SOC) or no Neoral + SOC. The primary endpoint is disease severity based on the World Health Organization (WHO) COVID Ordinal Outcomes Scale, on day 14. Secondary endpoints include safety and changes in serum inflammatory markers.

Condition or disease	Intervention/treatment	Phase
SARS (Disease)	Drug: Cyclosporine Other: Standard of Care Treatment	Phase 2

▶ Show detailed description

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	75 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Phase IIa clinical trial in which 75 non-ICU hospital inpatients will be randomized 2:1 to 7 days of Neoral (2.5mg/kg PO BID) + standard of care (SOC) or no CSA + SOC.
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Randomized Phase IIa Clinical Trial Of Cyclosporine For The Treatment Of **COVID-19**(+) Non-ICU Hospital Inpatients
Actual Study Start Date :	November 23, 2020
Estimated Primary Completion Date :	November 23, 2025
Estimated Study Completion Date :	November 23, 2025

Resource links provided by the National Library of Medicine

NIH NLM

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Arm A Cyclosporine Neoral, N=50 Patients 2.5 mg/kg PO BID 7 days	Drug: Cyclosporine 2.5 mg/kg PO BID 7 days Other Name: Neoral
Arm B Standard of Care Standard of Care Treatment, N= 25 Patients 7 days	Other: Standard of Care Treatment Standard of Care Treatment, N= 25 Patients, 7 days

Outcome Measures

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Primary Outcome Measures :

1. WHO COVID-19 clinical severity scale [Time Frame: Through study completion, an average of 1 month.]

   WHO COVID-19 clinical severity scale. Score 0-9. 0=Uninfected, 8=Death.

Eligibility Criteria

Go to

Information from the National Library of Medicine

NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years to 90 Years (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

3.1.1 Laboratory-confirmed SARS-CoV-2 infection within the past 10 days.

3.1.2 Patients admitted to non-ICU hospital floors or in an emergency department awaiting admission to a non-ICU hospital bed.

3.1.3 WHO COVID Scale Score 4 (Oxygen by mask or nasal prongs or WHO COVID Scale Score 5 (non-invasive ventilation or high-flow oxygen).

3.1.4 Age 18 to 90 years old.

3.1.5 ECOG (Eastern Cooperative Oncology Group) performance status ≤2 (see Appendix A).

3.1.6 Patients receiving or who have received standard of care therapy for COVID-19 can be included. This includes Remdesivir, Dexamethasone (or other steroids), and convalescent plasma.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria:

3.2.1 Allergy and/or hypersensitivity to CSA.

3.2.2 GFR<30 mL/min

Exclusion Criteria:

3.2.1 Allergy and/or hypersensitivity to CSA.

3.2.2 GFR<30 mL/min.

3.2.3 ALT (Alanine transaminase) or AST (Aspartate transaminase) >3X upper limits of normal.

3.2.4 Resistant hypertension (BP>140/90 mm Hg despite adherence to maximal doses of three antihypertensive agents).

3.2.5 Active bacterial or mycobacterial infection.

3.2.6 Pregnant and/or nursing patients. 3.2.7 Participation in a COVID-19 therapeutic drug trial.

3.2.8 Patients who have received or who are receiving anti-viral medications including hydroxychloroquine will not be excluded.

3.2.9 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Total cholesterol is < 100 (increased risk of seizure)

3.2.11 Concomitant dosing with Tacrolimus is a relative contraindication (increases overall immunosuppression and decrease seizure threshold

3.2.12 Concomitant malignancy is a relative contraindication (Neoral can increase susceptibility to development of neoplasia)

3.2.13 Inability to swallow oral medication

3.2.14 Treatment with immunomodulators or immunosuppressant drugs, including but not limited to IL-6 inhibitors, TNF inhibitors, anti-IL-1 agents, and JAK inhibitors.

3.2.15 Investigational Antiviral agents

Contacts and Locations

Go to

Clinical Trial to Evaluate Methylprednisolone Pulses and Tacrolimus in Patients With COVID-19 Lung Injury (TACROVID)

ClinicalTrials.gov Identifier: NCT04341038

Recruitment Status : Recruiting
First Posted : April 10, 2020
Last Update Posted : April 10, 2020

See Contacts and Locations

Sponsor:
Hospital Universitari de Bellvitge

Collaborator:
Institut d'Investigació Biomèdica de Bellvitge

Information provided by (Responsible Party):
Xavier Solanich, Hospital Universitari de Bellvitge

Brief Summary:

The primary objective of the study is to evaluate the days until reaching clinical stability after starting randomization in hospitalized patients with elevated inflammatory parameters and severe COVID-19 lung injury.

Condition or disease	Intervention/treatment	Phase
COVID-19 Lung Injury	Drug: Tacrolimus Drug: Methylprednisolone	Phase 3

Detailed Description:

Unfortunately, the treatment of COVID-19 disease is still based on life support therapies. Nowadays, there is no scientific evidence from clinical trials regarding the efficacy or safety of different drugs to treat COVID-19 patients, despite some of them evolving to fatal severe lung injury due to important inflammatory process secondary to pro-inflammatory cytokines. Interestingly, Tacrolimus has been shown to inhibit both pro-inflammatory cytokines and, also, human coronavirus SARS-Cov replication, but it has not specifically been tested in COVID-19 patients.

Our working hypothesis is that severe SARS-CoV-2 (COVID-19) pneumonia is secondary to a deleterious inflammatory process; so, the use of Methylprednisolone pulses and Tacrolimus in hospitalized severe COVID-19 lung injury patients might have a positive clinical effect.

Given the COVID-19 current health emergency, this study could provide useful evidence to treat some COVID-19 patients with Methylprednisolona and Tacrolimus, which might represent a new therapeutic option for them. Tacrolimus is a drug with more than 20 years of experience, and therefore, its side effects are well known and usually reversible. In addition, since tacrolimus is a low-cost and easy to produce at large-scale drug, it could be used to treat a large number of patients. The administration of this drugs could not only decrease mortality secondary to lung involvement by COVID-19, but also decrease the excessive burden of care that intensive care units are bearing.

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	84 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Outcomes Assessor)
Masking Description:	The statistician who will finally carry out the analyses will be blind to the treatment received by the patients
Primary Purpose:	Treatment

Arm	Intervention/treatment
Experimental: Intervention Methylprednisolone pulses 120mg/day for 3 consecutive days (if they were not previously administered) with Tacrolimus at the necessary dose to achieve plasma levels of 8-10 ng/ml. In addition, these patients can receive all the treatments considered necessary for their clinical management.	Drug: Tacrolimus the necessary dose to obtain blood levels of 8-10 ng / ml Other Name: Advagraf®, Modigraf® Drug: Methylprednisolone 120mg of methylprednisolone daily for 3 consecutive days Other Name: Urbason®, Solu-Moderín®
No Intervention: Usual care These patients can receive all the treatments considered necessary for their clinical management, except cyclosporine and tacrolimus.	

Outcome Measures

Go to

Primary Outcome Measures :

1. Time to reach clinical stability [Time Frame: 28 days]

   Assess the days until clinical stability is achieved after initiating randomization in hospitalized patients with elevated inflammatory parameters and severe COVID-19 lung injury.

   Clinical stability is defined if all the following criteria are met for 48 consecutive hours: Body temperature ≤ 37.0ºC; PaO2 / FiO2> 400 and / or SatO2 / FiO2> 300; Respiratory rate ≤ 24 rpm

Secondary Outcome Measures :

1. Time to reach an afebrile state for 48 hours. [Time Frame: 56 days]

   days