Study of Immunomodulation Using Naltrexone and Ketamine for COVID-19 (SINK COVID-19)

ClinicalTrials.gov Identifier: NCT04365985

Recruitment Status : Recruiting
First Posted : April 28, 2020
Last Update Posted : July 2, 2020

See Contacts and Locations

Sponsor:
William Beaumont Hospitals

Information provided by (Responsible Party):
Matthew Sims, MD, PhD, William Beaumont Hospitals

How to Read a Study Record

Study Description

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Brief Summary:

Ideal new treatments for Novel Coronavirus-19 (COVID-19) would help halt the progression disease in patients with mild disease prior to the need for artificial respiration (ventilators), and also provide a rescue treatment for patients with severe disease, while also being affordable and available in quantities sufficient to treat large numbers of infected people. Low doses of Naltrexone, a drug approved for treating alcoholism and opiate addiction, as well as Ketamine, a drug approved as an anesthetic, may be able to interrupt the inflammation that causes the worst COVID-19 symptoms and prove an effective new treatment. This study will investigate their effectiveness in a randomized, blinded trial versus standard treatment plus placebo.

Condition or disease	Intervention/treatment	Phase
COVID-19 Acute Respiratory Distress Syndrome Severe Acute Respiratory Syndrome (SARS) Coronavirus Infections	Drug: Naltrexone Drug: Ketamine Other: Placebo	Phase 2

Detailed Description:

There is an urgent need to develop new treatments for Novel Coronavirus-19 (COVID-19) infection using easily available and affordable medications. We need to develop a treatment protocol which prevents progression of the disease and a treatment protocol to rescue those with advanced disease. In addition to anti-viral therapeutics currently under investigation in other trials, the addition of immunomodulators to the treatment regimen appears have to potential to act as agents which can reduce the pathogenicity of this disease by reducing the dysregulation of autoimmunity which is destructive of normal tissue and when unchecked rapidly leads to mortality.

COVID-19 infection has three stages and 80% of infected people stay in stage 1 or stage 2A (viral response and early pulmonary effects), however 20% of patients progress to stage 2B (late pulmonary effects), and of those about 20% progress to stage 3 (hyper-inflammation). An ideal treatment for COVID-19 would have a two-pronged strategy: a treatment that would slow or interrupt the progression of the disease from mild/moderate (stage 1-2A) to severe (stage 2B-3), and a treatment to rescue patients who have become severe. Promising data using tocilizumab, an monoclonal antibody targeting the cytokine Interleukin-6 (IL-6), suggests that interrupting IL-6 is one of the potential pathways to accomplish this.

Low-dose naltrexone has been used off-label for treatment of pain and inflammation in multiple

sclerosis, Crohn's disease, fibromyalgia and other pain conditions. Lower than standard doses of naltrexone inhibit cellular proliferation of T- and B- cells and block Toll-like receptor 4 (TLR4), providing pain relief and anti-inflammatory benefit. Naltrexone at doses below the normal therapeutic dose appears to reduce production of multiple cytokines including IL-6 in a steady pace and is available as an oral preparation. As such it is ideal to use to attempt to modify progression to stage 2B as it can easily be given to both hospitalized patients and patients in the community.

Ketamine at low doses, below the normal anesthetic dose, appears to rapidly reduce the production of pro-inflammatory cytokines, especially IL-6 and tumor necrosis factor alpha (TNFα), for hours after an event which would induce the inflammatory response. This drug is given intravenously (IV), either by drip or push, and is easily given in a hospital environment. This could not easily be used in the community but could act as a rescue drug with lower cost and easier availability than tocilizumab, a monoclonal antibody targeting IL-6. Ketamine has been extensively studied in a variety of settings and indications with a well-established side-effect and dosing profile. Ketamine is generally well tolerated and remains inexpensive and widely available on the U.S. market and available for immediate use.

The trial will measure the ability of low dose naltrexone to reduce the progression of participants with COVID-19. In this study, naltrexone or placebo will be given to participants in early stages of COVID-19 infection in a randomized, double blinded manner, whereas the use of ketamine will be unblinded and given as a rescue agent should a participant progress. Additionally, should a participant be ineligible for the randomized portion of the study due to already being in a more advanced stage of the disease, they will be given the opportunity to enter the trial to receive ketamine without being randomized to naltrexone vs placebo.

Participants will continue to receive any standard of care COVID-19 treatment during their participation in this study. Laboratory blood tests such as IL-6 concentration, blood counts, liver and renal function panels as well as close physician supervision will be used to monitor participant condition during hospitalization. Participants will be contacted 1 month post discharge to evaluate outcomes and potential side effects.

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	500 participants
Allocation:	Randomized
Intervention Model:	Factorial Assignment
Intervention Model Description:	Prospective, single center, randomized, double blinded study of naltrexone with an open label extension using ketamine as a rescue drug for patients who progress in their disease
Masking:	Triple (Participant, Care Provider, Investigator)
Masking Description:	No other parties blinded

Primary Purpose:	Treatment
Official Title:	Study of Immunomodulation Using Naltrexone and Ketamine for COVID-19
Actual Study Start Date :	April 29, 2020
Estimated Primary Completion Date :	May 2021
Estimated Study Completion Date :	August 2021

Resource links provided by the National Library of Medicine NIH NLM

Drug Information available for: Ketamine Naltrexone Naltrexone hydrochloride

Genetic and Rare Diseases Information Center resources: Severe Acute Respiratory Syndrome Respiratory Distress Syndrome, Infant Acute Respiratory Distress Syndrome

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Placebo Comparator: Placebo Placebo by mouth 1 time per day for patients with stage I or stage 2A COVID-19	Other: Placebo Oral placebo, given from date of admission through time participant is stable for discharge for inpatient participants in mild/moderate COVID-19 infection stages. Placebo will continue for 1 month post discharge. Participants progressing to requirement for advanced oxygenation will be reassigned to Ketamine arm. Other Name: sugar pill
Experimental: Naltrexone Naltrexone 4.5 mg by mouth 1 time per day for patients with stage I or stage 2A COVID-19.	Drug: Naltrexone Low dose naltrexone, 4.5 mg by mouth, given from date of admission through time participant is stable for discharge for inpatient participants with mild/moderate COVID-19 infection stages. Naltrexone will

Arm	Intervention/treatment
	continue for 1 month post hospital discharge. Patients progressing to requirement for advanced oxygenation will be reassess when sedation and assigned to Ketamine arm. Naltrexone may be reduced to 1.5 mg/day if interfering with sedation and can be held when sedation and symptoms of withdrawal is an issue.. Other Names: • ReVia • Vivitrol
Experimental: Ketamine Ketamine IV infusion (0.15 mg/kg based on total body weight for maximum 20 mg every 6 hours) for patients with stage 2B or stage 3 COVID-19; may be increased to 0.3 mg/kg based on total body weight for a maximum of 30 mg every 6 hours if needed. Patients entering this arm from the placebo or naltrexone arms remain on those medications as well.	Drug: Naltrexone Low dose naltrexone, 4.5 mg by mouth, given from date of admission through time participant is stable for discharge for inpatient participants with mild/moderate COVID-19 infection stages. Naltrexone will continue for 1 month post hospital discharge. Patients progressing to requirement for advanced oxygenation will be reassess when sedation and assigned to Ketamine arm. Naltrexone may be reduced to 1.5 mg/day if interfering with sedation and can be held when sedation and symptoms of withdrawal is an issue.. Other Names: • ReVia • Vivitrol Drug: Ketamine Low dose ketamine hydrochloride given intravenously at a dosage of 0.15 mg/kg body weight for maximum 20 mg every 6 hours, to inpatient participants with

Arm	Intervention/treatment
	advanced oxygenation requirements from either time of admission or time of progression of mild/moderate disease until time participant is stable for discharge, as a rescue treatment. If patient is transferred from the naltrexone or placebo arm, they will continue to receive naltrexone/placebo. Dosage of ketamine may be increased to 0.3 mg/kg body weight, maximum 30 mg every 6 hours, if participant does not respond at the lower dosage. Ketamine can be reduced back to 0.15 mg/kg at the clinical decision of the investigator and when patient has hypertensive emergency, the dose can be held until hypertensive emergency is controlled. Other Name: Ketalar Other: Placebo Oral placebo, given from date of admission through time participant is stable for discharge for inpatient participants in mild/moderate COVID-19 infection stages. Placebo will continue for 1 month post discharge. Participants progressing to requirement for advanced oxygenation will be reassigned to Ketamine arm. Other Name: sugar pill

Outcome Measures

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Primary Outcome Measures :

1. Progression of oxygenation needs [Time Frame: up to 1 month]

   Count of participants initially presenting with mild/moderate disease who progress to requiring advanced oxygenation (high flow nasal canula, non-rebreather, continuous positive airway

pressure (CPAP), bilevel positive airway pressure (BIPAP), or intubation)

Secondary Outcome Measures :

1. Renal failure [Time Frame: up to 1 month]

   Count of participants who develop or experience worsened renal failure as defined by RIFLE criteria, a 5-point scale where the categories are labeled: Risk-Injury-Failure-Loss-End stage renal disease, with Risk being the least severe and End stage renal disease being the most severe. The criteria for determination of stage are factors of serum creatinine and urine output. Numbers of participants worsening one or more RIFLE stages will be reported.

2. Liver failure [Time Frame: up to 1 month]

   Count of participants who develop or experience worsened liver failure as defined by serum transaminases five times normal limits

3. Cytokine Storm [Time Frame: up to 1 month]

   Count of participants who develop cytokine storm as measured by elevated markers of inflammation (elevated D-dimer, hypofibrinogenemia, hyperferritinemia), evidence of acute respiratory distress syndrome (ARDS) measured by imaging findings and mechanical ventilator requirements, and/or continuous fever (≥ 38.1 ° Celsius unremitting)

4. Mortality [Time Frame: up to 1 month post hospital discharge]

   Count of participants who die from COVID-19

5. Length of hospital stay [Time Frame: up to 1 month]

   Length of hospital stay in days

6. Intensive Care Unit (ICU) admission [Time Frame: up to 1 month]

   Count of patients admitted to the ICU at any time during index hospitalization

7. Intensive Care Unit (ICU) duration [Time Frame: up to 1 month]

   Length of ICU stay in days

8. Intubation [Time Frame: up to 1 month]

   Count of participants requiring intubation

9. Intubation duration [Time Frame: up to 1 month]

   Length of intubation, measured in days

10. Time until recovery [Time Frame: up to 1 month]

    Time measured in days from hospital admission to determination patient is stable for discharge

Eligibility Criteria

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

Criteria

Inclusion Criteria:

- Positive for COVID -19
- Stage 1 or stage 2A COVID-19 for randomization to either placebo or naloxone arm OR Stage 2B or stage 3 COVID-19 for placement in ketamine arm
- Admitted to Beaumont Hospital - Royal Oak, Michigan
- Age ≥18
- Receiving ≤ 6 liters/minute oxygen by nasal cannula for randomization to either placebo or naloxone arm OR receiving ≥ 6 liters/minute oxygen by nasal cannula or requiring advanced oxygenation for placement in ketamine arm

Exclusion Criteria:

- Known allergy to naltrexone
- Known allergy to ketamine
- Diagnosis of schizophrenia or pyschosis
- Pregnancy based on available medical history, existing labs, or verbal report
- On chronic high dose opioids > 90mg morphine mg equivalence
- Use of tocilizumab chronically for arthritis or for COVID-19 treatment

Contacts and Locations

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Information from the National Library of Medicine NIH NLM

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Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT04365985***

Contacts

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Locations

United States, Michigan

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Sponsors and Collaborators

William Beaumont Hospitals

Investigators

Principal Investigator: Matthew Sims, MD PhD Beaumont Health

More Information

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Responsible Party:	Matthew Sims, MD, PhD, Director Infectious Disease Research, Beaumont Health; Professor of Internal Medicine and Foundational Medical Studies, OUWB School of Medicine, William Beaumont Hospitals
ClinicalTrials.gov Identifier:	NCT04365985 History of Changes
Other Study ID Numbers:	2020-097
First Posted:	April 28, 2020 Key Record Dates
Last Update Posted:	July 2, 2020
Last Verified:	June 2020

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:	No

Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Product Manufactured in and Exported from the U.S.:	Yes

Keywords provided by Matthew Sims, MD, PhD, William Beaumont Hospitals:

- naltrexone
- ketamine
- cytokine storm
- Interleukin-2
- therapeutic treatment

Additional relevant MeSH terms:

Coronavirus Infections	RNA Virus Infections
Severe Acute Respiratory Syndrome	Virus Diseases
Respiratory Distress Syndrome, Newborn	Lung Injury
Respiratory Distress Syndrome, Adult	Respiratory Tract Infections
Acute Lung Injury	Naltrexone
Syndrome	Ketamine
Disease	Analgesics
Pathologic Processes	Sensory System Agents
Lung Diseases	Peripheral Nervous System Agents
Respiratory Tract Diseases	Physiological Effects of Drugs
Respiration Disorders	Anesthetics, Dissociative
Infant, Premature, Diseases	Anesthetics, Intravenous
Infant, Newborn, Diseases	Anesthetics, General

Coronaviridae Infections
Nidovirales Infections

Anesthetics
Central Nervous System Depressants