

type, and the S-type, which may be less virulent. However, since the difference between the two so-called strains is small, scientists have stated that the two identified strains cannot be considered to be separate strains. Accordingly, there is a critical need for improved compositions and therapeutically effective methods for treating and preventing Coronavirus infections, including SARS-CoV-2.

SUMMARY ~~OF THE INVENTION~~

[0004a] In one aspect, the present disclosure provides use of a GM-CSF antagonist in the manufacture of a medicament for treating a subject infected with 2019 coronavirus (SARS-CoV-2) and treating and/or preventing inflammation-induced lung injury in a subject infected with the coronavirus (SARS-CoV-2), wherein the GM-CSF antagonist is neutralizing anti-hGM-CSF antibody lenzilumab, Namilumab, Otilimab, Gimsilumab, or TJM2 (TJ003234); wherein the GM-CSF antagonist is anti-GM-CSF receptor antibody Mavrilimumab; or wherein the GM-CSF antagonist is chimeric GM-CSF neutralizing antibody KB002.

[0005] In one ~~aspect~~example, the present ~~invention~~disclosure provides a method for reducing time to clinical improvement or time to recovery of a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the time to clinical improvement or time to recovery of the subject is reduced by at least 40% compared to the time to clinical improvement or time to recovery of a control subject treated with standard of care and is not administered a GM-CSF antagonist, wherein the subject and the control subject each have severe or critical COVID-19 pneumonia.

[0006] In another ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours.

[0007] In another ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, and a therapeutically effective amount of an anti-viral agent.

[0008] In still another ~~aspect~~example, the present ~~invention~~disclosure provides a method for preventing and/or treating inflammation-induced lung injury in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours.

[0009] In one aspectexample, the present inventiondisclosure provides a method for preventing and/or treating inflammation-induced lung injury in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, and a therapeutically effective amount of an anti-viral agent.

[00010] In another aspectexample, the present inventiondisclosure provides a method for preventing and/or treating cytokine release syndrome (CRS) and/or toxicity induced by CRS, such as ARDS, myocarditis (including Kawasaki's Disease or Kawasaki Shock Syndrome), Multisystem Inflammatory Syndrome in Children (MIS-C), encephalopathy, and disseminated intravascular coagulation (DIC), in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours.

[00011] In one aspectexample, the present inventiondisclosure provides a method for preventing and/or treating cytokine release syndrome (CRS) and/or toxicity induced by CRS, such as ARDS, myocarditis (including Kawasaki's Disease or Kawasaki Shock Syndrome), Multisystem Inflammatory Syndrome in Children (MIS-C), encephalopathy, and disseminated intravascular coagulation (DIC), in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, and a therapeutically effective amount of anti-viral agent.

[00012] In another aspectexample, the present inventiondisclosure provides a method for treating a subject infected with a coronavirus (SARS-CoV-2) comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, and a therapeutically effective amount of an oxygen transporter.

[00013] In yet another aspectexample, the present inventiondisclosure provides a method for treating and/or preventing inflammation-induced lung injury in a subject infected with a coronavirus (SARS-CoV-2) comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical

composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, and a therapeutically effective amount of an oxygen transporter.

[00013a] In one aspect, the present disclosure provides use of a GM-CSF antagonist in the manufacture of a medicament for predicting and preventing a cytokine release syndrome (CRS) and/or inflammation-induced lung injury (ARDS) in a subject infected with 2019 coronavirus (SARS-CoV-2), wherein the GM-CSF antagonist is neutralizing anti-hGM-CSF antibody lenzilumab; wherein the GM-CSF antagonist is an anti-GM-CSF antibody selected from the group consisting of Namilumab, Otilimab, Gimsilumab, and TJM2 (TJ003234); wherein the GM-CSF antagonist is chimeric GM-CSF neutralizing antibody KB002; or wherein the GM-CSF antagonist is anti-GM-CSF receptor antibody Mavrilimumab; the use further comprising:

- a) measuring a level of oxygen saturation by pulse oximetry (SpO₂) of the subject and/or
- b) performing a chest x-ray or computed tomography (CT) scan,

wherein a measured level of the SpO₂ of $\leq 94\%$ and/or presence of airspace opacity on chest x-ray or ground-glass opacity on CT scan indicate the subject has COVID-19 pneumonia, and

- (i) the subject has CRS or is at high risk of developing CRS; and/or
- (ii) the subject has a severe risk factor for developing ARDS,

wherein the subject has CRS or is at high risk of developing CRS, wherein the high risk of developing CRS is a risk that is 2.3 times greater than the risk of developing CRS when a measured level of the SpO₂ is $> 94\%$ and/or the subject does not have dyspnea and/or has clear lungs on chest x-ray or on CT scan, and/or the subject has the severe risk for developing ARDS, wherein the severe risk for developing ARDS is 2.3 times greater than the risk for developing ARDS when a measured level of the SpO₂ is $> 94\%$ and/or the subject does not have dyspnea and/or has clear lungs on chest x-ray or on CT scan; and

c) wherein a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist is to be administered to (i) the subject having CRS or at high risk of developing CRS and/or (ii) the subject having the severe risk factor for developing ARDS, wherein the pharmaceutical composition comprises the GM-CSF antagonist at a dose of from 1200 mg to 1800 mg for administration over 24 hours.

[00014] In one aspectexample, the present inventiondisclosure provides a method for predicting and preventing a cytokine release syndrome (CRS) and/or inflammation-induced lung injury (ARDS) in a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising: a) measuring a level of serum ferritin in a blood sample obtained from the subject, wherein a measured level of the serum ferritin of > 300 mcg/L indicates (i) the subject has CRS or is at high risk of developing CRS; and/or (ii) the subject has a severe risk factor for developing ARDS, wherein the severe risk for developing ARDS is a risk that is three times greater than the risk for developing ARDS when a measured level of the serum ferritin is < 300 mcg/L in a blood sample obtained from a subject; and b) administering to (i) the subject having CRS or at high risk of developing CRS and/or (ii) the subject having the severe risk factor for developing ARDS a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours.

[00015] In another aspectexample, the present inventiondisclosure provides a method for predicting and preventing a cytokine release syndrome (CRS) and/or inflammation-induced lung injury (ARDS) in a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising: a) measuring a level of oxygen saturation by pulse oximetry (SpO_2) of the subject and/or b) performing a chest x-ray or computed tomography (CT) scan, wherein a measured level of the SpO_2 of $\leq 94\%$ and/or presence of airspace opacity on chest x-ray or ground-glass opacity on CT scan indicate the subject has COVID-19 pneumonia, and (i) the subject has CRS or is at high risk of developing CRS; and/or (ii) the subject has a severe risk factor for developing ARDS, wherein the subject has CRS or is at high risk of developing CRS, wherein the high risk of developing CRS is a risk that is 2.3 times greater than the risk of developing CRS, when a measured level of the SpO_2 of $> 94\%$ and/or the subject does not have dyspnea and/or has clear lungs on chest x-ray or on CT scan, and/or the subject has the severe risk for developing ARDS, wherein the severe risk for developing ARDS is 2.3 times greater than the risk for developing ARDS when a measured level of the SpO_2 of $> 94\%$ and/or the subject does not have dyspnea and/or has clear lungs on chest x-ray or on CT scan; and c) administering to (i) the subject having CRS or at high risk of developing CRS and/or (ii) the subject having the severe risk factor for developing ARDS a pharmaceutical composition

comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours.

[00016] In another aspectexample, the present inventiondisclosure provides a method for treating a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist.

[00017] In still another aspectexample, the present inventiondisclosure provides a method for treating a subject infected with 2019 coronavirus (SARS-CoV-2), the method comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist and a therapeutically effective amount of an anti-viral agent. Combination therapy comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist further comprises administering a second drug, including one or more anti-viral agent(s), an anti-SARS-CoV-2 vaccine, human immunoglobulin (IVIG), monoclonal neutralizing antibodies, and serum containing human polyclonal antibodies to SARS-CoV-2, and a toll-like receptor (TLR) agonist.

[00018] In one aspectexample, the present inventiondisclosure provides a method for preventing and/or treating inflammation-induced lung injury in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist.

[00019] In a further aspectexample, the present inventiondisclosure provides a method for preventing and/or treating inflammation-induced lung injury in a subject in need thereof, the method comprising administering to the subject a GM-CSF antagonist and an anti-viral agent.

[00020] In one aspectexample, the present inventiondisclosure provides a method for preventing and/or treating cytokine release syndrome (CRS) and/or toxicity induced by CRS, such as ARDS, myocarditis (including Kawasaki's Disease or Kawasaki Shock Syndrome), Multisystem Inflammatory Syndrome in Children (MIS-C), encephalopathy, and disseminated intravascular coagulation (DIC), in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist. In specific embodimentexamples, the subject in need of prevention and/or treatment of CRS and/or toxicity induced by CRS is a subject infected with 2019 coronavirus (SARS-CoV-2).

[00021] In another aspectexample, the present inventiondisclosure provides a method for preventing and/or treating cytokine release syndrome (CRS) and/or toxicity induced by CRS, such as ARDS, myocarditis (including Kawasaki's Disease or Kawasaki Shock Syndrome), Multisystem Inflammatory Syndrome in Children (MIS-C), encephalopathy, and disseminated intravascular coagulation

(DIC), in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist and a therapeutically effective amount of an anti-viral agent. In particular embodiment examples, the subject in need of prevention and/or treatment of CRS and/or toxicity induced by CRS is a subject infected with 2019 coronavirus (SARS-CoV-2).

[00022] In another aspect example, the present invention disclosure provides a method for treating a subject infected with a coronavirus (SARS-CoV-2) comprising administering to the subject a therapeutically effective amount of GM-CSF antagonist and a therapeutically effective amount of an oxygen transporter.

[00023] In yet another aspect example, the present invention disclosure provides a method for treating and/or preventing inflammation-induced lung injury in a subject infected with a coronavirus (SARS-CoV-2) comprising administering to the subject a therapeutically effective amount of a GM-CSF antagonist and a therapeutically effective amount of an oxygen transporter.

[00023a] In one aspect, the present disclosure provides use of a GM-CSF antagonist in the manufacture of a medicament for reducing time to recovery of a subject infected with 2019 coronavirus (SARS-CoV-2) and alleviating the immune-mediated CRS in the subject, wherein the medicament comprises a pharmaceutical composition comprising a therapeutically effective amount of the GM-CSF antagonist, wherein the pharmaceutical composition comprises a dose of from 1200 mg to 1800 mg for administration over 24 hours, wherein the time to recovery of the subject is reduced by at least 33% compared to time to recovery of a second subject administered a therapeutically effective amount of an antiviral agent without administration of a GM-CSF antagonist; wherein the GM-CSF antagonist is neutralizing anti-hGM-CSF antibody lenzilumab, Namilumab, Otilimab, Gimsilumab, and TJM2 (TJ003234); wherein the GM-CSF antagonist is anti-GM-CSF receptor antibody Mavrilimumab; or wherein the GM-CSF antagonist is chimeric GM-CSF neutralizing antibody KB002.

[00023b] In one aspect, the present disclosure provides use of a GM-CSF antagonist in the manufacture of a medicament for reducing time to clinical improvement or time to recovery of a subject infected with 2019 coronavirus (SARS-CoV-2), wherein the medicament comprises a pharmaceutical composition comprising a therapeutically effective amount of the GM-CSF antagonist, wherein the GM-CSF antagonist is neutralizing anti-hGM-CSF antibody lenzilumab, Namilumab, Otilimab, Gimsilumab, or TJM2 (TJ003234); anti-GM-CSF receptor antibody Mavrimumab; chimeric GM-CSF neutralizing antibody KB002 or mouse antibody LMM102, wherein the time to clinical improvement or time to recovery of the subject is reduced by at least 40% compared to the time to clinical improvement or time to recovery of a control subject treated with standard of care and is not administered a GM-CSF antagonist, wherein the subject and the control subject each have severe or critical COVID-19 pneumonia;

wherein the clinical improvement comprises at least two points on an 8-point ordinal clinical outcome scale and time to recovery comprises obtaining/reaching a 6, 7, or 8 score wherein the 8-point ordinal outcome scale is a clinical status of the subject consisting of scores: 1) death; 2) hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, not requiring supplemental oxygen and requiring ongoing medical care; 6) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; 7) not hospitalized and having a limitation of activities; and 8) not hospitalized and having no limitations of activities; and

wherein the COVID-19 pneumonia is severe COVID-19 pneumonia as determined by radiographic assessment or by low-flow oxygen requirement or wherein the COVID-19 pneumonia is critical COVID-19 pneumonia as determined by the need for high-flow oxygen or non-invasive positive pressure ventilation support.

[00024] In another ~~aspect~~example, the present ~~invention~~disclosure provides a method for reducing time to recovery of a subject infected with 2019 coronavirus (SARS-CoV-2) and alleviating the immune-mediated CRS in the subject, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist, wherein the pharmaceutical composition is administered at a dose of from 1200 mg to 1800 mg over 24 hours, wherein the time to recovery of the subject is reduced by at least 33%

compared to time to recovery of a second subject administered a therapeutically effective amount of an antiviral agent without administration of a GM-CSF antagonist.

[00024a] In one aspect, the present disclosure refers to use of a GM-CSF antagonist in the manufacture of a medicament for treating a subject infected with 2019 coronavirus (SARS-CoV-2) for a time period beyond an initial acute hyper-inflammatory period, wherein the medicament comprises a pharmaceutical composition comprising a therapeutically effective amount of the GM-CSF antagonist, wherein the GM-CSF antagonist is anti-hGM-CSF antibody lenzilumab, Namilumab, Otilimab, Gimsilumab, or TJM2 (TJ003234); or the GM-CSF antagonist is anti-GM-CSF alpha receptor antibody Mavrilimumab;

wherein the time period beyond the initial acute hyper-inflammatory period is from 21 days to 13 weeks after onset of the initial acute hyper-inflammatory period;

wherein the initial acute hyper-inflammatory period occurs about 5 to 12 days after onset of symptoms of infection with SARS-CoV-2;

wherein the symptoms of infection with SARS-CoV-2 occur 2 to 14 day after exposure to SARS-CoV-2, wherein the symptoms of infection with SARS-CoV-2 comprise fever, chills, cough without fever, shortness of breath, difficulty breathing, fatigue, muscle aches, body aches, headache, back ache, loss of taste and/or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea, abdominal pain, or combinations thereof.

[00025] In another ~~aspect~~example, the present ~~invention~~disclosure provides a method for treating a subject infected with 2019 coronavirus (SARS-CoV-2) for a time period beyond an initial acute hyper-inflammatory period, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a GM-CSF antagonist.

[00026] Other features and advantages of this ~~invention~~disclosure will become apparent from the following detailed description, examples, and figures. It should be understood, however, that the detailed description and the specific examples while indicating preferred ~~embodiment~~examples are given by way of illustration only, since various changes and modifications within the spirit and scope of the ~~invention~~disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS