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Methods of Treating Infection and Symptoms Caused by SARS-CoV-2 Using Lithium

Abstract

The present inventive concept provides methods of using lithium to treat infection and symptoms caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and other pathogenic microbial organisms through direct application of lithium to areas of the respiratory tract. Lithium-based formulations and kits including the same for the treatment of respiratory infections and symptoms thereof are also provided.

Methods of Treating Infection and Symptoms Caused by SARS-CoV-2 Using Lithium

Field

[0001] The present inventive concept provides methods of using lithium to treat infection and symptoms caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and other pathogenic microbial organisms affecting the respiratory tract.

Background

[0002] As disclosed in PCT/US2020/038736, the contents of which are incorporated herein by reference, formulations including lithium can be used for the prevention and treatment of inflammatory conditions, gout, joint disease and pain, and symptoms thereof.

[0003] Mulligan et al., 1993 demonstrated that a murine antibody to human IL-8 had protective effects in inflammatory lung injury in rats. The inflammatory lung injury was linked to E-selectin-dependent recruitment of neutrophils in rats. It was found that an antibody to human IL-8 protected against this lung injury by blocking the recruitment of neutrophils. Harrison, et al., 2007 in *Avian Pathology* demonstrated that LiCl inhibits infectious coronavirus bronchitis in cell culture. Also, Chang, J Immunol 2004, showed that the up-regulation of IL-8 release by SARS-CoV is induced at the transcriptional level via mRNA. The overproduction of cytokines and the CC chemokine IL-8 are the hallmark of the SARS virus; and facilitates transendothelial migration of polymorphonuclear leukocytes (PMNs).

[0004] The cytokine storm seen in Covid-19 appears to involve the lung tissue. This contributes to the majority of fatalities, necessitating ventilator support. The severity and outcomes associated with Covid-19 infections may be directly related to circulating (and local) levels of IL-8. Also, IL-8 is important in inflammatory lung diseases like bronchial asthma or severe infections by Respiratory Syncytial Virus (RSV). Puthothu, et al. , *Clin Mol Allergy* 2006.

Summary

[0005] According to embodiments of the present inventive concept, lithium formulations can be used to mitigate viral infections, such as coronavirus infection, and symptoms thereof. Direct application of lithium to the respiratory tract can be used to mitigate such viral infections. Lithium can be used to modulate protein kinase signaling cascades. Lithium can be effective against IL-8 and leucocyte/monocyte recruitment. Lithium can be used to provide a protective anti-apoptotic effect on cellular death. Further, lithium-based formulations and kits including the same for the treatment of infection and symptoms thereof are also provided.

Detailed Description

[0006] The present inventive concept provides methods of using lithium and lithium formulations to prevent or treat infection and symptoms caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and other pathogenic microbial organisms that affect the respiratory tract. The methods of using lithium can also be used to prevent or treat bronchiolitis, asthma, RSV, influenza, cystic fibrosis, chronic obstructive pulmonary disease and pulmonary fibrosis and symptoms thereof.

[0007] The "respiratory tract" as used herein refers to the respiratory organ system responsible for the exchange of oxygen and carbon dioxide and, in humans, spans from the nostrils to the lung alveoli. The respiratory tract is divided into the upper respiratory tract (URT) and the lower respiratory tract (LRT). The URT generally includes the nose, nasal passages, paranasal sinuses, the nasopharynx and oropharynx and the portion of the larynx above the vocal cords. The LRT generally includes the portion of the larynx below the vocal cords, the trachea, smaller airways (that is, bronchi and bronchioli) and alveolar ducts, alveolar sacs and alveoli.

[0008] The term "prevent," "preventing" or "prevention of" (and grammatical variations thereof) refers to prevention and/or delay of the onset and/or progression of a disease, disorder and/or a clinical symptom(s) in a subject and/or a reduction in the severity of the onset and/or progression of the disease, disorder and/or clinical symptom(s) relative to what would occur in the absence of the methods of the inventive concept. The prevention can be complete, e.g., the total absence of the disease, disorder and/or clinical

symptom(s). The prevention can also be partial, such that the occurrence of the disease, disorder and/or clinical symptom(s) in the subject and/or the severity of onset and/or the progression are less than what would occur in the absence of carrying out the steps of the methods of the present invention.

[0009] As used herein, the expression "treat," "treating" "treatment of" (and grammatical variations thereof) infection means improving, reducing, or alleviating at least one symptom or biological consequence of the infection in a subject, and/or reducing or decreasing virus titer, load, replication or proliferation in a subject following exposure to the virus. The expression "treating infection" also includes shortening the time period during which a subject exhibits at least one symptom or biological consequence of virus infection after being infected by a virus. The subject may exhibit or be diagnosed with one or more symptoms or biological consequences of virus infection.

[0010] A "therapeutically effective amount," "treatment effective amount" and "effective amount" as used herein are synonymous unless otherwise indicated, and mean an amount of a composition or formulation of the present inventive concept that is sufficient to improve the condition, disease, or disorder being treated and/or achieved the desired benefit or goals as described herein. Those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. Similarly, a "prevention effective" amount is an amount that is sufficient to prevent (as defined herein) the disease, disorder and/or clinical symptom in the subject. Those skilled in the art will appreciate that the level of prevention need not be complete, as long as some benefit is provided to the subject.

[0011] Interleukin 8 (IL8) also known as chemokine (C-X-C motif) ligand 8, CXCL8) is a member of the chemokine family and is produced by a wide range of cell types like monocytes, macrophages, fibroblasts and ceratinocytes.

[0012] In particular embodiments, the virus or virus symptoms prevented or treated according to the present inventive concept is any virus belonging to the Coronaviridae family now known or yet to be discovered. Exemplary coronaviruses include 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus associated with Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus associated with severe acute

respiratory syndrome, or SARS) and SARS-CoV-2 (the novel coronavirus associated with coronavirus disease 2019, or COVID-19). In still other embodiments, the virus or virus symptoms prevented or treated according to the present inventive concept is the Human orthopneumovirus (also known as human respiratory syncytial virus, or HRSV, or RSV).

[0013] "Subject" as used herein may be a patient or individual. In some embodiments, the subject is a human; however, a subject of this disclosure can include an animal subject, particularly mammalian subjects such as canines, felines, bovines, caprines, equines, ovines, porcines, rodents (e.g. rats and mice), lagomorphs, primates (including non-human primates), etc., including domesticated animals, companion animals and wild animals for veterinary medicine, treatment or pharmaceutical drug development purposes.

[0014] The subjects relevant to this disclosure may be male or female and may be any species and of any race or ethnicity, including, but not limited to, Caucasian, African-American, African, Asian, Hispanic, Indian, etc., and combined backgrounds. The subjects may be of any age, including newborn, neonate, infant, child, adolescent, adult, and geriatric.

[0015] In some embodiments, the subject is at high risk for contracting a coronavirus. In some embodiments, the subject is aged 65 or older, has high blood pressure, asthma, lung disease, diabetes, heart disease, kidney disease, lung disease, cancer and/or is immunocompromised. In some embodiments, the subject is an infant, and in some cases, a premature infant.

[0016] Further, the subject can be a patient in a medical facility, hospital setting, ambulatory care setting, urgent or critical care setting, emergency medical services setting, and the like. In some embodiments, the subject is transitioning to a step-down, discharge or outpatient status. In some embodiments, the subject is a discharged patient. In some embodiments, the subject is not in a healthcare setting.

[0017] In particular embodiments, lithium, an active ingredient in the formulations of the present inventive concept, includes, but is not limited to, elemental lithium, lithium ion, a lithium salt, a lithium derivative, etc. In some embodiments, lithium is elemental lithium, a lithium mimetic, lithium acetate, lithium aluminate, lithium aluminum hydride, lithium amide, lithium aspartate, lithium azide, lithium beryllide, lithium bis(trifluoromethanesulfonyl)imide, lithium

bis(trimethylsilyl)amide, lithium borate, lithium borohydride, lithium bromide, lithium carbide, lithium carbonate, lithium chlorate, lithium chloride, lithium citrate, lithium cobalt oxide, lithium cyanide, lithium diisopropylamide, lithium disilicate, lithiumfluoride, lithium hexafluorogermanate, lithium hexafluorophosphate, lithium hydride, lithium hydroxide, lithium hypochlorite, lithium imide, lithium iodate, lithium iodide, lithium iridate, lithium iron phosphate, lithium lactate, lithium metaborate, lithium metasilicate, lithium methoxide, lithium molybdate, lithium molybdenum purple bronze, lithium monoxide anion, lithium nickel cobalt aluminum oxides, lithium nickel manganese cobalt oxides, lithium niobate, lithium nitrate, lithium nitride, lithium nitrite, lithium orotate, lithium orthosilicate, lithium oxide, lithium perchlorate, lithium peroxide, lithium platinate, lithium polonide, lithium ruthenate, lithium salicylate, lithium selenide, lithium stearate, lithium succinate, lithium sulfate, lithium sulfide, lithium sulfite, lithium superoxide, lithium tantalate, lithium tetrachloroaluminate, lithium tetrafluoroborate, lithium tetrahydridogallate, lithium tetrakis(pentafluorophenyl)borate, lithium tetramethylpiperidide, lithium titanate, lithium triborate, lithium triethylborohydride, lithium triflate or lithium tungstate. In some embodiments, lithium is lithium carbonate, lithium citrate, lithium salicylate or lithium lactate.

[0018] In terms of administration, the most suitable route (parenteral, oral, nasal, inhalational, ocular, transmucosal and transdermal) in any given case will depend on the nature and severity of the condition being treated and the pharmaceutical formulation being administered. In particular embodiments, routes of administration are inhalation including nasal and oral inhalation, nasal delivery through administration to the nasal epithelium, oral delivery (capsules, tablets, aqueous suspensions or solutions, etc.) and parenteral injection such as intravenous delivery and infusion. In particular embodiments, routes of administration include nasal, inhalational, intratracheal, intrapulmonary and intrabronchial. In particular embodiments, dosage forms include, for example, dispersions, suspensions, solutions, syrups, granules, beads, powders, pellets, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, and the like. In particular embodiments, lithium is administered by nebulizer, inhaler, foam, mist, positive pressure ventilation, endotracheal tube, gel, or other suitable vehicle directly to lung tissue and/or into the bronchial tree. In such cases, the affected epithelium and/or localized vasculature is directly affected. In particular embodiments,

alveolar structures are subjected to lithium to stop anti-inflammatory reactions and infiltration from the endothelium into the lung tissue.

[0019] Due to the critical nature of the patients being administered the lithium therapy, the course may be short, for example less than two weeks, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days. Toxicity levels of lithium would be closely monitored.

[0020] In certain embodiments, in addition to lithium, the formulations of the present inventive concept may include at least one adjuvant such as a penetration enhancer, anti-oxidant, stabilizer, carrier, or vehicle. In certain embodiments, the compositions including lithium and the pharmaceutically acceptable carrier will typically contain on the order of about 0.001 to about 99.9% by weight lithium, in some embodiments, 0.01 wt. % to 90 wt. % lithium, 1 wt. % to about 80.0 wt. %, 1 wt. % to about 50.0 wt. %, or about 1 wt. % to about 30 wt. % lithium, with the remainder of the composition including a pharmaceutically acceptable carrier and/or an additional therapeutic agent for the treatment of respiratory disorders. As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the inventive concept, and not injurious to the patient.

[0021] Embodiments of the present inventive concept further include concomitant administration to the subject of an effective amount of a respiratory disorder agent along with administration of the composition including lithium in a pharmaceutically acceptable carrier. The terms "concomitant administration", "concomitantly administering" and "combination therapy" refer to the administration of two or more agents in any manner in which the pharmacological effects of those agents are manifested in the subject at the same time. These terms encompass administering two or more agents to a subject substantially concurrently, for example in a single dosage form (e.g. a solution, spray,

foam, gel, paste, cream, ointment, lotion, serum, oil, liniment, aerosol, liquid, sheet, patch, ampule, syringe, etc.), administering at least one agent in one dosage form and the other agent(s) in a separate dosage form, and administering each agent in its own separate dosage form. The administration may be performed sequentially or simultaneously. For example, for sequential administration, the first agent may be administered before or after the second agent. In some embodiments, concomitant administration includes concurrent administration. In other embodiments, concomitant administration includes sequential administration.

[0022] In particular embodiments, lithium may be administered concomitantly with any therapeutic agent used to treat a respiratory disorder including, but not limited to, COVID-19, RSV, influenza, asthma, bronchiolitis, cystic fibrosis, chronic obstructive pulmonary disease and/or pulmonary fibrosis and symptoms thereof. In some embodiments, the therapeutic agent includes, but is not limited to, zinc, a non-steroidal anti-inflammatory drug (NSAID; e.g., aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, etc.), antibiotics, azithromycin, antiviral medications, a neuraminidase inhibitor, hydroxychloroquine, chloroquine, histamine 2 receptor antagonists (e.g. famotidine), steroid treatment (e.g., dexamethasone), and Vitamin C.

[0023] In further embodiments, administration of lithium may be provided in combination with supportive care, including oxygen therapy or supplemental oxygen, continuous positive airway pressure (CPAP) or Heated humidified high-flow (HHHF) therapy, high flow nasal cannula(e) (HFNC) or high flow nasal oxygen (HFNO).

[0024] The present inventive concept further provides kits or an assembly of components packaged together with optional instructions (written, audio or visual) regarding how to use the components of the kit. The kits may include all components of the elements described herein for mitigation of respiratory disorders and/or symptoms thereof, or a subset of the elements in any combination. The kit may include packaging materials that may maintain the components and can be composed of material commonly used for such purposes (e.g., paper, corrugated fiber, glass, plastic, foil, ampules, vials, tubes, bottles, syringes, etc.). In addition to including lithium as an active pharmaceutical ingredient, a kit may also contain the therapeutic agents used to treat respiratory disorders as described above. In some embodiments, the kits are sterile.

[0025] The foregoing is meant to be illustrative of exemplary embodiments of the inventive concept and are not to be construed as limiting thereof. It will be understood that modifications, substitutions, and alternatives will be apparent to one of ordinary skill in the art. Such modifications, substitutions, and alternatives can be made without departing from the spirit and scope of the inventive concept, which should be determined from the appended claims.

Methods of Treating Infection and Symptoms Caused by SARS-CoV-2 Using Lithium

Claims:

1. A method of preventing, treating or controlling a viral infection or symptoms thereof in a subject comprising administering to a respiratory tract or portion thereof of the subject a composition comprising lithium.

2. The method of claim 1, wherein the viral infection or symptoms thereof is caused by a virus belonging to the Coronaviridae family.

3. The method of claim 1, wherein the viral infection or symptoms thereof is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or *Human orthopneumovirus* (HRSV or RSV).

4. The method of claim 1, wherein the subject is a human subject.

5. The method of claim 1, wherein the subject is infected with a virus belonging to the Coronaviridae family.

6. The method of claim 1, wherein the subject is infected with SARS2 or RSV.

7. The method of claim 1, wherein the subject is afflicted with COVID-19 or RSV.

8. The method of claim 1, wherein the lithium is elemental lithium, a lithium mimetic, lithium acetate, lithium aluminate, lithium aluminum hydride, lithium amide, lithium aspartate, lithium azide, lithium beryllide, lithium bis(trifluoromethanesulfonyl)imide, lithium

bis(trimethylsilyl)amide, lithium borate, lithium borohydride, lithium bromide, lithium carbide, lithium carbonate, lithium chlorate, lithium chloride, lithium citrate, lithium cobalt oxide, lithium cyanide, lithium diisopropylamide, lithium disilicate, lithiumfluoride, lithium hexafluorogermanate, lithium hexafluorophosphate, lithium hydride, lithium hydroxide, lithium hypochlorite, lithium imide, lithium iodate, lithium iodide, lithium iridate, lithium iron phosphate, lithium lactate, lithium metaborate, lithium metasilicate, lithium methoxide, lithium molybdate, lithium molybdenum purple bronze, lithium monoxide anion, lithium nickel cobalt aluminum oxides, lithium nickel manganese cobalt oxides, lithium niobate, lithium nitrate, lithium nitride, lithium nitrite, lithium orotate, lithium orthosilicate, lithium oxide, lithium perchlorate, lithium peroxide, lithium platinate, lithium polonide, lithium ruthenate, lithium salicylate, lithium selenide, lithium stearate, lithium succinate, lithium sulfate, lithium sulfide, lithium sulfite, lithium superoxide, lithium tantalate, lithium tetrachloroaluminate, lithium tetrafluoroborate, lithium tetrahydridogallate, lithium tetrakis(pentafluorophenyl)borate, lithium tetramethylpiperidide, lithium titanate, lithium triborate, lithium triethylborohydride, lithium triflate or lithium tungstate.

9. The method of claim 1, wherein the lithium is administered directly to the nasal passages, paranasal sinuses, nasopharynx, oropharynx, larynx trachea, bronchi, bronchioli, alveolar ducts, alveolar sacs and/or alveoli of the subject.

10. The method of claim 1, wherein the lithium is co-administered with at least one of zinc, a non-steroidal anti-inflammatory agent, an antibiotic, azithromycin, an antiviral medication, a neuraminidase inhibitor, hydroxychloriquine, chloriquine, a histamine 2 receptor antagonist, steroid treatment, Vitamin C and oxygen therapy.

11. An inhalational lithium formulation comprising:

lithium; and

a pharmaceutically acceptable carrier.

12. The formulation of claim 11, wherein the formulation is a dispersion, mist, suspension, solution, spray, dry powder or aerosol.

13. The formulation of claim 11 further comprising at least one of zinc, a non-steroidal anti-inflammatory agent, an antibiotic, azithromycin, an antiviral medication, a neuraminidase inhibitor, hydroxychloriquine, chloriquine, a histamine 2 receptor antagonist, a steroid drug and Vitamin C.

14. A kit comprising:

a formulation of claim 11;

optionally at least one of zinc, a non-steroidal anti-inflammatory agent, an antibiotic, azithromycin, an antiviral medication, a neuraminidase inhibitor, hydroxychloriquine, chloriquine, a histamine 2 receptor antagonist, a steroid drug and Vitamin C; and

optionally instructions for the use of the components of the kit.

15. The inventive concept as substantively disclosed herein.

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Document Description: COVID-19 Collab Database Request for Prov Appl

PTO/SB/452 (09-20)

CERTIFICATION AND REQUEST FOR COVID-19 PROVISIONAL PATENT APPLICATION PROGRAM

(Page 1 of 1)

First Named Inventor:	Carl Ganio
Title of Invention:	Methods of Treating Infection and Symptoms Caused by SARS-CoV-2 Using Lithium
Contact information to include in database (optional)	Carl Ganio, drcarlganio@twc.com, 772-633-3104

APPLICANT HEREBY MAKES THE FOLLOWING CERTIFICATIONS AND REQUESTS THAT THE USPTO INCLUDE THE DESCRIPTION OF THE ACCOMPANYING PROVISIONAL PATENT APPLICATION IN A PUBLIC DATABASE.

1. The description of the accompanying provisional patent application concerns a product or process relating to COVID-19 and such product or process is subject to an applicable FDA approval for COVID-19 use.

2. The accompanying application is in the English language.

3. The accompanying application is being filed in DOCX format via the USPTO's Patent Center filing system, together with this form.

4. The applicant understands that while the required filing fee for the accompanying provisional application may be deferred by acceptance into this program, the appropriate filing fee must be paid in order for a subsequent U.S. nonprovisional application to claim the benefit of the filing date of the accompanying provisional application. Applicant recognizes that the filing fee due in the future may be more than the current fee due and that by deferring payment of the filing fee, there may be an increase in the total fee due.

5. Applicant authorizes and requests that the description, including the specification and any drawings, claims and/or abstract of the accompanying provisional patent application, as well as this form, be included in a searchable online public database.

6. Applicant understands that inclusion in the public database is a publication of the description and this form.

Signature /Shawna C. Lemon/	Date October 5, 2020
Name (Print/Typed) Shawna C. Lemon	Practitioner Registration Number 53888

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.