BRIEF SUMMARY

In one aspect, the present disclosure refers to use of a substance consisting of a structural analogue of the AQGV peptide with a length in the range of 4- 12 amino acids that comprises at least 50%, more preferably at least 75%, most preferably at least 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), proline (P), and arginine (R) in the manufacture of a medicament for reducing the permeability of an endothelial layer of a blood vessel in a subject suffering from a viral infection caused by COVID-19 or a mutant thereof, wherein the substance is to be provided via an infusion to the endothelial layer and reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of the viral infection.

In another aspect, the present disclosure refers to a pharmaceutical formulation for use as disclosed herein, comprising an AQGV peptide, or a structural analogue thereof and an excipient suitable for parenteral administration.

In one example, the present disclosure refers to use of a substance in the manufacture of a medicament for reducing the permeability of an endothelial layer of a blood vessel in a subject, wherein the substance is to be provided to the endothelial layer and reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection. In one example, the present disclosure also refers to a pharmaceutical formulation for any one of the uses disclosed herein.

In a first example, the disclosure provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, such as with a virus. In a preferred example, the disclosure provides said method for reducing the gas diffusion distance between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from a respiratory infection, allowing reduction of fluid in alveoli and/or allowing improved oxygen supply to the subject's body. In a preferred example, said substance comprises an AQGV-peptide, an LQGV-peptide, or a functional analogue of either. In a preferred example, the disclosure provides said method for reducing the gas diffusion distance between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from an infection with a respiratory virus. It is moreover preferred that said viral infection is caused by a virus requiring a specific receptor and a more ubiquitous binding partner present on at least a percentage of lung alveolar cells. In one preferred example, it is preferred that said specific receptor is ACE-2. In another preferred example, it is preferred that the more ubiquitous binding partner is a glycoprotein comprising a sialic acid residue. It is in particular preferred that said ubiquitous binding partner binds with a fMLF-like amino acid sequence, for

example wherein said sequence at least comprises a membrane-proximal-external-region (MPER, herein also identified as fusogenic sequence). It is in particular preferred that said virus is a coronavirus, in particular a coronavirus with an MPER as identified in figure 11, more in particular at least comprising a fusogenic sequence as identified in figure 12. It is most preferred that said MPER at least comprises amino acid sequence KWPWIWL (amino acids identified herein by one-letter code). In a further preferred example, the disclosure provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, such as with a virus, wherein the coronavirus is the COVID-19 virus (SARS-COV-2) or a mutant thereof.

lab-specific type drawn, and not all labs report the same units providing various acceptable ranges for the results. There are many things that can cause elevated D-dimer beyond venous thromboembolism (VTE), such as age or pregnancy. The D-dimer half-life of 8 hours results in elevated levels for approximately 3 days after the inciting event. Quantitative D-dimer holds a sensitivity of 94% to 98%, yet only specificity of 50% to 60%. This allows to utilize it as a screening tool but requires clinical evidence from the history and physical examination, preferably with intermittent repeated testing to confirm the diagnosis or follow a patient's health status.

Thus, the disclosure in one example provides a method for reducing the permeability of an endothelial layer of a blood vessel comprising providing to the layer a substance reducing the ratio of angiopoietin-2 to angiopoietin-1 at the site of increased permeability as a result of an infection. In one example this method serves to reduce the gas diffusion distance (or at least to prevent increasing the diffusion distance) between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from a respiratory infection, in particular patients with underlying disease causing limited oxygen availability. Reduced vascular permeability in patients suffering vascular leakage is generally associated with reduced D-dimer levels. According to the disclosure, in one example the substances to be used in the methods according to the disclosure include peptides that influence hemodynamics, particularly by influencing gap junctions between the cells. Such peptides include AQGV and functional analogues thereof. A functional analogue is defined as a substance that provides the same or a similar function (in kind, not necessarily in amount). Basically, any substance that decreases permeability of the vascular system may be used according to the present disclosure. For one, tetrapeptide AQGV (herein also referred to as EA-230) has surprisingly been found to modulate vascular permeability to the good. In particular, EA-230 significantly improves hemodynamic stability in humans, even in the absence of inflammatory activity of the patient. Permeability governs the amount of fluid leaking from blood vessels. Administration of fluid therapy generally increases leakage. Based on Phase II trial patient observations, we found a significant reduction of adverse fluid retention (fluid leakage) in patients treated with EA-230 ($p = 0.03$). Throughout clinical trials, EA-230 was shown to be safe and well tolerated. EA-230 shows significant improvements in patient recovery, over placebo patient. EA-230 treated patients are released faster from intensive care ($p=0.0232$) and hospital ($p=0.0015$).

CLAIMS

1. Use of a substance consisting of a structural analogue of the AQGV peptide with a length in the range of 4- 12 amino acids that comprises at least 50%, more preferably at least 75%, most preferably at least 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), proline (P), and arginine (R) in the manufacture of a medicament for reducing the permeability of an endothelial layer of a blood vessel in a subject suffering from a viral infection caused by COVID-19 or a mutant thereof, wherein the substance is to be provided via an infusion to the endothelial layer and reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of the viral infection.

2. The use according to claim 1, for reducing the gas diffusion distance between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from a respiratory infection.

3. The use according to claim 1 or 2, wherein the substance consists of an AQGV peptide, or a structural analogue consisting of peptides comprising (i) a tetrapeptide selected from the group of AQLP, PLQA, LQGV, LAGV, PQVG, PQVA, PQVR, VGQL, LQPL, RQGV, LQVG, LQGA, LQGR, AQGA, QPLA, PQVP, VGQA, QVGQ, and VGQG, or (ii) other permutations of peptides of 4-12 amino acids constituted of particularly the amino acids of the above tetrapeptides.

4. The use according to any one of the previous claims, wherein the substance is to be administered intravenously, preferably at a rate of at least 75mg/kg/hr, or more preferably at least 90 mg/kg/hr.

5. The use according to any one of the previous claims, wherein the substance is to be administered intermittently by dosing for 2-4 hours of at least 75mg/kg/hr, then optionally

reducing to 30mg/kg/hour for 2-4 hours or stop administering the substance for 1-2 hours and then resume treatment with 2-4 hours of at least 75mg/kg/hr.

6. The use according to any one of the previous claims, wherein the subject is to be monitored for haemodynamic stability.

7. The use according to any one of the previous claims, wherein an antiviral agent is to be further administered to the subject.

8. A pharmaceutical formulation for use according to any one of the preceding claims, comprising an AQGV peptide, or a structural analogue thereof and an excipient suitable for parenteral administration.