Administration of ADM in combination with ADM-binding-Protein-1 is described for treatment of sepsis and septic shock in the art. It is assumed that treatment of septic animals with ADM and ADM-binding-Protein-1 prevents transition to the late phase of sepsis. It has to be noted that in a living organism ADM binding protein (complement factor H) is present in the circulation of said organism in high concentrations (Pio *et al.*: Identification, characterization, and physiological actions of complement factor H as an Adrenomedullin binding Protein present in Human Plasma; Microscopy Res. and Technique, 55:23-27 (2002) and Martinez *et al.*; Mapping of the Adrenomedullin-Binding domains in Human Complement factor H; Hypertens Res Vol. 26, Suppl (2003), S56-59).

In accordance with the invention the ADM-binding-Protein-1 may be also referred to as ADM-binding-Protein-1 (complement factor H).

Prevention or reduction of organ dysfunction or organ failure is very important when treating a patient having a chronic or acute disease or acute condition, especially a life threatening disease or condition.

Summary

In one aspect, there is provided the use of anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for prevention or reduction of organ dysfunction or prevention of organ failure in said patient, wherein said antibody or antibody fragment or non-Ig scaffold binds to region of at least 4 amino acids within sequence of aa 1-42 of mature human ADM (SEQ ID NO: 24), and wherein said organ is selected from the group consisting of heart, kidney, liver, lung, pancreas, small intestines and spleen.

~~In another aspect, there is provided the use of a pharmaceutical formulation comprising an anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient as disclosed herein.~~

Description of the invention

Subject matter of the present invention is an anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a chronic

Claims

1. Use of anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for prevention or reduction of organ dysfunction or prevention of organ failure in said patient, wherein said antibody or antibody fragment or non-Ig scaffold binds to region of at least 4 amino acids within sequence of aa 1-42 of mature human ADM (SEQ ID NO: 24), and wherein said organ is selected from the group consisting of heart, kidney, liver, lung, pancreas, small intestines and spleen.

2. The use according to claim 1, wherein said anti-ADM antibody or said anti-adrenomedullin antibody fragment or said anti-ADM non-Ig scaffold is a non-neutralizing ADM antibody or a non-neutralizing adrenomedullin antibody fragment or a non-neutralizing ADM non-Ig scaffold.

3. The use according to claim 1 or 2, wherein said organ is kidney or liver.

4. The use according to claim 1 ~~or to~~ ~~2~~3, wherein said organ is heart.

5. The use according to any of the claims 1 to 4, wherein said antibody or fragment or scaffold binds to the N-terminal part, ~~(~~aa 1-21,~~)~~ of mature adrenomedullin.

6. The use according to any of claims 1 to 5, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

7. The use according any of claims 1 to 6, wherein said antibody or fragment or scaffold exhibits a binding affinitity to ADM of at least 10^{-7} M.

8. The use according any of claims 1 to 7, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1, ~~(~~complement factor H~~)~~.

9. The use according to any of claims 1 to 8, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end, ~~(~~aa1,~~)~~ of mature adrenomedullin.

10. The use according to any of claims 1 to 9, wherein said antibody or said fragment or scaffold is an ADM stabilizing antibody or fragment or scaffold that enhances the half life, ~~(~~t1/2 half retention time,~~)~~ of adrenomedullin in serum, blood, plasma at least 10 %, ~~preferably~~ or at least 50 %, or~~more preferably~~ >50 %, or~~most preferably~~ >100%.

11. The use according to any of claims 1 to 10, wherein said antibody or fragment or scaffold blocks the ADM bioactivity not more than 80 %, ~~preferably~~ or not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

12. The use according to any of claims 1 to 11, wherein said organ dysfunction or organ failure is caused by a disease ~~is~~ selected from the group consisting of ~~comprising~~ sepsis, diabetes, cancer, heart failure, and shock.

13. The use according to any of claims 1 to 12, wherein said acute disease is not SIRS, sepsis, or septic shock.

14. The use according to any of claims 1 to 13, wherein said antibody or fragment is a human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof wherein the heavy chain comprises the sequences

SEQ ID NO: 1
GYTFSRYW

SEQ ID NO: 2
ILPGSGST

SEQ ID NO: 3
TEGYEYDGFDY

and wherein the light chain comprises the sequences

SEQ ID NO:4
QSIVYSNGNTY

SEQ ID NO: 5
RVS

SEQ ID NO: 6
FQGSHIPYT.

15. The use according to claim 14, wherein the anti-ADM antibody is a human monospecific anti-ADM antibody, wherein said antibody or fragment comprises the sequences:

SEQ ID NO: 7 (AM-VH-C)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGSTNY
NEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTTLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 8 (AM-VH1)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 9 (AM-VH2-E40)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 10 (AM-VH3-T26-E55)
QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
SEQ ID NO: 11 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

SEQ ID NO: 12 (AM-VL-C)

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRFSG
VPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 14 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

16. The use according to any of claims 1 to 15, wherein said antibody or fragment or scaffold is a modulating antibody or fragment or scaffold that enhances the half life ~~,~~ (t1/2 half retention time~~,~~) of adrenomedullin in serum, blood, plasma at least 10 %, ~~preferably~~ or at least 50 %, or~~more preferably~~ >50 %, or~~most preferably~~ >100% and that blocks the ADM bioactivity not more than 80 %, or ~~preferably~~ not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

17. The use according to any of the claims 1 to 16, wherein the medicament is to be used in combination with vasopressors.

18. The use according to claim 17, wherein the vasopressors are ~~e.g.~~ catecholamine and/ or fluids to be administered intravenously.

1918. The use according to any of the claims 1 to 1817, wherein the medicament is to be used in combination with ADM binding protein and/or further active ingredients.

~~19. Use of a pharmaceutical formulation comprising an anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient according to any of claims 1 to 18.~~

~~20. The use according to claim 19, wherein said pharmaceutical formulation is a solution , preferably a ready-to-use solution.~~

~~21. The use according to claim 20, wherein said pharmaceutical formulation is in a freeze-dried state.~~

~~22. The use according to any of claims 19 to 21, wherein said pharmaceutical formulation is to be administered intra-muscular.~~

~~23. The use according to any of claims 19 to 21, wherein said pharmaceutical formulation is to be administered intra-vascular.~~

~~24. The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered via infusion.~~

~~25. The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered systemically to a patient for prevention or reduction of organ dysfunction or organ failure in a patient having an acute disease or acute condition.~~

~~26. The use according to claims 19 to 21, wherein said pharmaceutical formulation is to be administered systemically via infusion to a patient for prevention or reduction of organ dysfunction or organ failure in a patient having an acute disease or acute condition.~~