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 the prevention or reduction of organ dysfunction or prevention of organ failure in a patient, wherein said antibody or antibody fragment or non-Ig scaffold binds to region of at least 4 amino acids within sequence of aa 1-21 of mature human ADM (SEQ ID NO: 23), and wherein said organ is selected from the group consisting of heart, kidney, liver, lung, pancreas, small intestines and spleen.

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 the prevention or reduction of organ dysfunction or prevention of organ failure in a patient, wherein said antibody or antibody fragment or non-Ig scaffold binds to region of at least 4 amino acids within sequence of aa 1-21 of mature human ADM (SEQ ID NO: 23), 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 patient is suffering from a disease or condition selected from the group consisting of severe infections, Systemic Inflammatory Response-Syndrome (SIRS), sepsis, diabetes, cancer, acute and chronic vascular diseases, shock, organ dysfunction, burnings, surgery, traumata, poisoning and damages induced by chemotherapy.

3. The use according to claim 2, wherein the acute and chronic vascular disease is selected from the group consisting of heart failure, myocardial infarction, stroke and atherosclerosis.

4. The use according to claim 2, wherein the shock is septic shock.

5. The use according to any of claims 1 to 4, 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.

6. The use according to any of claims 1 to 5, wherein said organ is kidney or liver.

7. The use according to any of claims 1 to 5, wherein said organ is heart.

8. The use according to any of the claims 1 to 7, wherein said antibody or fragment or scaffold binds to the N-terminal part, aa 1-21, of mature adrenomedullin.

9. The use according to any of claims 1 to 8, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

10. The use according any of claims 1 to 9, wherein said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M, and wherein said binding affinity is determined according to Example 1.

11. The use according any of claims 1 to 10, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1, complement factor H.

12. The use according to any of claims 1 to 11, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end, aa1, of mature adrenomedullin.

13. The use according to any of claims 1 to 12, 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 %, or at least 50 %, or >50 %, or >100%.

14. The use according to any of claims 1 to 13, wherein said antibody or fragment or scaffold blocks the ADM bioactivity not more than 80 %, or not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

15. The use according to any of claims 1 to 14, wherein said organ dysfunction or organ failure is caused by a disease selected from the group consisting of sepsis, diabetes, cancer, heart failure, and shock.

16. The use according to any of claims 1 to 15, wherein said acute disease is not SIRS, sepsis, or septic shock.

17. The use according to any of claims 1 to 16, 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.

18. The use according to claim 17, 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

19. The use according to any of claims 1 to 18, 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 %, or at least 50 %, or >50 %, or >100% and that blocks the ADM bioactivity not more than 80 %, or not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

20. The use according to any of the claims 1 to 19, wherein the medicament is to be used in combination with vasopressors.

21. The use according to claim 20, wherein the vasopressors are catecholamine and/ or fluids to be administered intravenously.

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22. The use according to any of the claims 1 to 21, wherein the medicament is to be used in combination with ADM binding protein and/or further active ingredients.