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).

Summary

In one aspect, there is provided the use of anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig-protein scaffold in the manufacture of a medicament for therapy or prevention of SIRS, ~~a severe infection~~meningitis, sepsis, shock e.g. septic shock in a patient for the reduction of the mortality risk for said patient wherein said antibody or fragment binds to the N-terminal part, aa 1-21, of adrenomedullin YRQSMNNFQGLRSFGCRFGTC ; SEQ ID No. 23~~or scaffold is a non-neutralizing anti-ADM antibody or a non-neutralizing anti-adrenomedullin antibody fragment or a non-neutralizing anti-ADM non-Ig scaffold~~.

In another aspect, there is provided the use of a pharmaceutical formulation in the manufacture of a medicament for therapy or prevention of SIRS, ~~a severe infection~~meningitis, sepsis, shock e.g. septic shock in a patient for the reduction of the mortality risk for said patient, wherein said pharmaceutical formulation comprises an antibody or fragment or scaffold as disclosed herein.

Description of the invention

According to the present invention it has been found that the administration of an anti-ADM antibody or anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to ADM may reduce considerably the risk of mortality in a patient having a severe acute disease or acute condition.

Throughout the specification the "antibodies", or "antibody fragments" or "non-Ig scaffolds" in accordance with the invention are capable to bind ADM, and thus are directed against ADM, and thus can be referred to as "anti-ADM antibodies", "anti-ADM antibody fragments", or "anti-ADM non-Ig scaffolds".

CLAIMS

1. Use of anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig-protein scaffold in the manufacture of a medicament for therapy or prevention of SIRS, ~~a severe infection~~meningitis, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient wherein said antibody or fragment ~~or scaffold is a non-neutralizing anti-ADM antibody or a non-neutralizing anti-adrenomedullin antibody fragment or a non-neutralizing anti-ADM non-Ig scaffold~~binds to the N-terminal part, aa 1-21, of adrenomedullin

   YRQSMNNFQGLRSFGCRFGTC ; SEQ ID No. 23.

2. The use according claim 1, wherein said antibody or antibody fragment or non-Ig-protein scaffold is monospecific.

3. The use according to any of claims 1 or 2, wherein said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M.

4. The use according to any of claims 1 to 3, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1, ~~(~~complement factor H~~)~~.

~~5. The use according to any of claims 1 to 4, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of preferably at least 4, or at least 5 amino acids within the sequence of aa 1-42 of mature human ADM:~~

~~YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA~~
~~(SEQ ID No.: 24).~~

~~6. The use according any of claims 1 to 5 wherein said antibody or fragment or scaffold binds to the N-terminal part (aa 1-21) of adrenomedullin:~~

~~YRQSMNNFQGLRSFGCRFGTC~~
~~(SEQ ID No. 23).~~

~~7.~~5. The use according to any of claims 1 to ~~6~~4, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end, ~~(~~aa 1~~)~~ of adrenomedullin.

~~8.~~6. The use according to any of claims 1 to ~~7~~5, characterized in that said antibody, antibody fragment or non-Ig-protein scaffold does not bind to the C-terminal portion of ADM, being it aa 43-52 of ADM

PRSKISPQGY-NH2 ~~(~~; SEQ ID NO: 25~~)~~.

~~9.~~7. The use according to any of claims 1 to ~~8~~6, wherein said antibody or 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 at least, 50 %, more preferably > 50 %, most preferably > 100 %.

~~10.~~8. The use according to any of claims 1 to ~~9~~7, wherein said antibody or fragment or scaffold blocks the bioactivity of ADM not more than 80 %, preferably not more than 50%, wherein the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

~~11.~~9. The use according to any of claims 1 to ~~10~~8, wherein said patient is an ICU patient.

~~12.~~10. The use according to any of claims 1 to ~~11~~9, 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.

~~13~~11. The use according to claim ~~12~~10, wherein said antibody or fragment is a human monoclonal antibody or fragment, wherein said antibody or fragment comprises a sequence selected from the group comprising:

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
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFD

YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH
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

~~14~~12. The use according to any of the claims 1 to ~~13~~11, wherein the medicament is to be used in combination with vasopressors *e.g.* catecholamine and/ or fluids administered intravenously.

~~15.~~13. The use according to any of the claims 1 to ~~14~~12, wherein the medicament is to be used in combination with ADM binding protein-1, ~~(~~complement factor H~~)~~ and/or further active ingredients.

~~16.~~14. Use of a pharmaceutical formulation in the manufacture of a medicament for therapy or prevention of SIRS, ~~a severe infection~~meningitis, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient, wherein said pharmaceutical formulation comprises an antibody or fragment or scaffold according to any of claims 1 to ~~14~~12.

~~17.~~15. The use according to claim ~~16~~14 wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.

~~18.~~16. The use according to claim ~~16~~14 wherein said pharmaceutical formulation is in a freeze-dried state.

~~19.~~17. The use according to any of claims ~~16~~14 to ~~17~~15, wherein said pharmaceutical formulation is to be administered intra-muscular.

~~20.~~18. The use according to any of claims ~~16~~14 to ~~17~~15, wherein said pharmaceutical formulation is to be administered intra-vascular.

19. The use according to claim ~~20~~18, wherein said pharmaceutical formulation is to be administered via infusion.

~~22~~20. The use according to any of the claims ~~16~~14 to ~~21~~19, wherein said pharmaceutical formulation is to be administered systemically.