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 scaffold in the manufacture of a medicament for therapy or prevention of SIRS, a severe infection, 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.

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, 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".

In accordance with the invention the administration of an anti-ADM antibody or anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to ADM is preferably a systemic application.

The patient being in such an acute disease or condition may have a co-morbidity like a chronical disease. The treatment according to the present invention aims especially the treatment of the acute disease or condition. It may be the treatment of an acute disease or condition in a patient having cancer, which does not mean necessarily that the cancer itself is treated.

Anti-Adrenomedullin (ADM) antibody is an antibody that binds specifically to ADM, anti-adrenomedullin antibody fragment is a fragment of an anti-ADM antibody wherein said fragment binds specifically to ADM. An anti-ADM non-Ig scaffold is a non-Ig scaffold that binds specifically to ADM. Specifically binding to ADM allows binding to other antigens as well. This means, this specificity would not exclude that the antibody may cross-react with other polypeptides than that against it has been raised. Said anti-adrenomedullin antibody or an anti-adrenomedullin antibody fragment binding to ADM or an anti-ADM non-Ig scaffold

CLAIMS

1. Use of ~~A~~anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold ~~for use~~ in the manufacture of a medicament for therapy or prevention of SIRS, a severe infection, 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.

2. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ The use according claim 1, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

3. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ 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. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ 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. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy or prevention of SIRS, sepsis, shock as *e.g.* septic shock in a patient~~ 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. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or an anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ 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. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or an anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 1 to 6, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end (aa 1) of adrenomedullin.

8. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 1 to 7, characterized in that said antibody, antibody fragment or non-Ig 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. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or an anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 1 to 8, 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. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or an anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 1 to 9, wherein said antibody or fragment or scaffold blocks the bioactivity of ADM not more than 80 %, preferably not more than 50%.

11. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or an anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ The use according to any of claims 1 to 10, wherein said patient is an ICU patient.

12. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 1 to 11, 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. ~~A human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof for use in therapy or prevention of SIRS, a severe infection, sepsis, shock e.g. septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to claim 12, 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. ~~Anti-ADM antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ The use according to any of the claims 1 to 13, wherein the medicament is to be used in combination with vasopressors *e.g.* catecholamine and/ or fluids administered intravenously.

15. ~~Anti-ADM antibody or anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient~~ The use according to any of the claims 1 to ~~13 or a combination according to claim~~ 14, wherein the medicament is to be used in combination with ADM binding protein-1 (complement factor H) and/or further active ingredients.

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

17. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to claim 16 wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.

18. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to claim 16 wherein said pharmaceutical formulation is in a freeze-dried state.

19. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 16 to 17, wherein said pharmaceutical formulation is to be administered intra-muscular.

20. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of claims 16 to 17, wherein said pharmaceutical formulation is to be administered intra-vascular.

21. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said~~

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

22. ~~Pharmaceutical formulation for use in therapy or prevention of SIRS, a severe infection, sepsis, shock *e.g.* septic shock in a patient for the reduction of the mortality risk for said patient~~ The use according to any of the claims 16 to 21, wherein said pharmaceutical formulation is to be administered systemically.