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).

Patients having a chronic or acute disease or acute condition, especially patients at the ICU (Intensive Care Unit), may suffer from fluid imbalance. This may cause severe adverse events such as kidney failure and mortality.

It was the subject of the present invention to provide a medicament for regulating the fluid balance and/or improving the fluid balance of such patients.

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 the regulation of fluid balance and 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).

In another aspect, there is provided the use of a pharmaceutical formulation comprising an 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 as disclosed herein.

Detailed Description

The expression "regulating fluid balance" with the context of the instant invention is directed to any correction of a manifested – imbalance – of a patient's fluid balance due to an underlying chronic or acute disease or acute condition. Said correction is in favour of re-establishing normotension in said patients. The person skilled in the art is fully aware that blood pressure in general, as well as hyper- and hypotension is closely related to the fluid balance of a patient.

Fluid balance is the balance of the input and the output of fluids in the body to allow metabolic processes to function. Dehydration is defined as a 1% or greater loss of body mass as a result of

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 the regulation of fluid balance and 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).

2. The use according to claim 1, wherein said patient is a patient in need of regulating the fluid balance.

~~3. The use according to claim 1 or 2, wherein said anti-ADM antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig 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.~~

~~4.~~3. The use according to any of claims 1 to ~~3~~2, wherein the medicament is for preventing or reducing edema in said patient.

~~5.~~4. The use according to any of claims 1 to ~~4~~3, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

~~6.~~5. The use according to any of claims 1 to

~~5~~4, characterized in that said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M.

~~7~~6. The use according to any of claims 1 to ~~6~~5, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1 (complement factor H).

~~8. The use according to any of claims 1 to 7, 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).~~

~~9~~7. The use according to any of claims 1 to ~~8~~6, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of at least 4 or 5 amino acids within the sequence of aa 1-21 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTC
(SEQ ID No. 23).

~~10~~8. The use according to any of claims 1 to ~~9~~7, wherein said antibody or fragment scaffold recognizes and binds to an epitope containing the N-terminal end amino acid 1 of mature human ADM and wherein said

antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified Adrenomedullin nor N-terminal degraded adrenomedullin.

~~11.~~9. The use according to any of claims 1 to ~~10~~8, wherein said antibody or fragment or scaffold is an ADM stabilizing antibody or ADM stabilizing antibody fragment or ADM stabilizing non-Ig scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, preferably at least 50 %, more preferably >50 %, most preferably >100 %.

~~12.~~10. The use according to any of claims 1 to ~~11~~9, wherein said antibody or fragment blocks the circulating ADM bioactivity not more than 80 %, preferably not more than 50% when the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor cAMP functional assay according to Example 2.

~~13.~~11. The use according to any of claims 1 to ~~12~~10, wherein said patient suffers from a disease that is selected from the group comprising SIRS, sepsis, diabetes, cancer, heart failure, shock and kidney dysfunction.

~~14.~~12. The use according to any of claims 1 to ~~13~~11, wherein said antibody or fragment is an antibody or fragment that binds to ADM or an antibody fragment thereof that binds to ADM 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.~~13. The use according to claim ~~14~~12, 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)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPG
SGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYW
GQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP
KHHHHHH
SEQ ID NO: 8 (AM-VH1)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILP
GSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDY
WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
EPKHHHHHH
SEQ ID NO: 9 (AM-VH2-E40)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILP
GSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDY
WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS

GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK
HHHHHH

SEQ ID NO: 10 (AM-VH3-T26-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSG
STNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGT
TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

SEQ ID NO: 11 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGS
GSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQG
TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKHHHHHH

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

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSN
RFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSN
RDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSN
RDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

~~16.~~14. The use according to any of claims 1 to ~~15~~13, wherein said antibody or fragment or scaffold is a modulating antibody or modulating fragment or modulating scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, preferably at least 50 %, more

preferably >50 %, most preferably >100 % and that blocks the bioactivity of ADM not more than 80 %, preferably not more than 50% when determining the bioactivity of ADM is determined in a human recombinant Adrenomedullin receptor CAMP functional assay according to Example 2.

~~17.~~15. The use according to any of the claims 1 to ~~16~~14, 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 (SEQ ID NO: 25)
PRSKISPQGY-NH2
(SEQ ID NO:25).

~~18.~~16. The use according to any of the claims 1 to ~~17~~15, wherein the medicament is to be used in combination with catecholamine and/ or fluids administered intravenously.

~~19.~~17. The use according to any of the claims 1 to ~~18~~16, wherein the medicament is to be used in combination with ADM binding protein and/or further active ingredients.

~~20.~~18. The use according to any of the preceding claims, characterized in that said therapy is not a method of primary treatment to said acute disease or acute condition.

~~21.~~19. Use of a pharmaceutical formulation comprising an 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 according to any of claims 1 to ~~20~~18.

~~22.~~20. The use according to claim ~~21~~19, wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.

~~23.~~21. The use according to claim ~~22~~20, wherein said pharmaceutical formulation is in a freeze-dried state.

~~24~~22. The use according to any of the claims ~~21–~~19 to ~~23~~21, wherein said pharmaceutical formulation is to be administered to a patient for regulating the systemic fluid balance with the proviso that said patient is in need of regulating the fluid balance.