The dose of tacrolimus or a close structural analogue thereof employed is less than that used to produce its clinical immunosuppressant effects when treating organ rejection or diseases such as arthritis or myasthenia gravis.

The use of tacrolimus for the treatment purposes described herein is presently preferred over that of a close structural analogue.

The mechanism by which tacrolimus or a close structural analogue provides it desirable effect in the present invention is not related to the mechanism by which it achieves immunosuppression. Indeed, use at conventional immunosuppressant doses are believed to be at best poorly ineffective. Tacrolimus and its close structural analogues have now been found to have a dose response curve with a pronounced bell shape with an upper cut off well below conventional immunosuppressant doses.

Brief Summary ~~of Invention~~

In one aspect of the present disclosure, there is provided tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells, wherein tacrolimus or its close structural analogue is administered not more than once a day in a dose which does not cause immunosuppression and which produces a trough whole blood level of tacrolimus or its close structural analogue of at least 0.05 ng/mL.

In another aspect of the present disclosure, there is provided the use of tacrolimus or its close structural analogue in the manufacture of a medicament for the treatment of a disease characterised by the deposition of protein aggregates in neuronal cells which medicament contains an amount of tacrolimus or its close structural analogue that when administered once per day dose not cause immunosuppression and which has a trough whole blood level of at least 0.05 ng/mL.

In a further aspect of the present disclosure, there is provided tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells wherein tacrolimus or its close structural analogue is administered once a day at a dose of 0.001 mg/kg to 0.02 mg/kg.

In another aspect of the present disclosure, there is provided the use of tacrolimus or a close structural analogue in the manufacture of a medicament for treating a disease characterised by protein aggregate deposition in neuronal cells wherein tacrolimus or its close structural analogue wherein the medicament contains 0.001 mg/kg to 0.02 mg/kg of tacrolimus or its close structural analogue.

In a further aspect of the present disclosure, there is provided tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition by administration not more than once a day of an amount which effects epigenetic modification which leads to an increase in autophagy and/or an improvement in oxidative stress.

In another aspect of the present disclosure, there is provided the use of tacrolimus or close structural analogue thereof in the manufacture of a medicament for the treatment of a disease characterised by protein aggregate deposition in neuronal cells by administration not more than once per day which medicament contains an amount of tacrolimus or close structural analogue thereof which effects epigenetic modification which leads to an increase in autophagy and/or an improvement in oxidative stress.

In a further aspect of the present disclosure, there is provided a unit dose pharmaceutical composition containing 0.05 mg to 1.3 mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier therefor for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells.

In another aspect of the present disclosure, there is provided a unit dose orally administrable pharmaceutical composition comprising 0.05 mg to 1.2 mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier for use in the treatment of a disease characterised by the deposition of protein aggregates in neuronal cells.

The present ~~invention~~ disclosure further provides a method of treating a disease characterised by protein aggregate deposition in neuronal cells which comprises administering to a human in need thereof not more than once a day an effective amount of tacrolimus or a close structural analogue thereof in a dose which does not cause immunosuppression and which produces a trough whole blood level of tacrolimus or its close structural analogue of at least 0.05 ng/mL.

Apt diseases for treatment by such a method include in particular ALS, Parkinson's disease, Alzheimer's disease and Huntington's disease.

Claims

~~1. A method of treating a disease characterised by protein aggregate deposition in neuronal cells which comprises administering to a human in need thereof not more than once a day an effective amount of tacrolimus or a close structural analogue thereof in a dose which does not cause immunosuppression and which produces a trough whole blood level of tacrolimus or its close structural analogue of at least 0.05 ng/mL.~~

~~2~~1. Tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells, wherein tacrolimus or its close structural analogue is administered not more than once a day in a dose which does not cause immunosuppression and which produces a trough whole blood level of tacrolimus or its close structural analogue of at least 0.05 ng/mL.

~~3~~2. The use of tacrolimus or its close structural analogue in the manufacture of a medicament for the treatment of a disease characterised by the deposition of protein aggregates in neuronal cells which medicament contains an amount of tacrolimus or its close structural analogue that when administered once per day dose not cause immunosuppression and which has a trough whole blood level of at least 0.05 ng/mL.

~~4~~3. A ~~method,~~ compound for use or use of a compound as claimed in ~~any of~~ claim~~s~~ 1 or ~~2 to 3~~ wherein the trough whole blood level is at least 0.075 ng/mL, at least 0.2 ng/mL or at least 0.3 ng/mL~~.~~, and/or

~~5. A method, compound for use or use of a compound as claimed in any of claims 1 to 4~~ wherein the trough whole blood level is less than 1.2 ng/mL, less than 1.1 ng/mL or less than 1.0 ng/mL.

~~6~~4. A ~~method,~~ compound for use or use of a compound as claimed in any of claims 1 to ~~5~~ 3 which employs tacrolimus.

~~7. A method of treating a disease characterised by protein aggregate deposition in neuronal cells which comprises administering to a human in need thereof not more than once a day an effective amount of tacrolimus or a close structural analogue thereof wherein the dose is from 0.001 mg/kg to 0.02 mg/kg.~~

~~8~~5. Tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells wherein tacrolimus or its close structural analogue is administered once a day at a dose of 0.001 mg/kg to 0.02 mg/kg.

~~9~~6. The use of tacrolimus or a close structural analogue in the manufacture of a medicament for treating a disease characterised by protein aggregate deposition in neuronal cells wherein tacrolimus or its close structural analogue wherein the medicament contains 0.001 mg/kg to 0.02 mg/kg of tacrolimus or its close structural analogue.

~~10~~7. A ~~method,~~ compound for use or use of a compound as claimed in ~~any of~~ claim~~s~~ ~~6~~ 4 or 5 ~~to 8~~ which employs 0.001 mg/kg to 0.02 mg/kg.

~~11~~8. A ~~method,~~ compound for use or use of a compound as claimed in any of claims ~~7~~ 5 to ~~10~~ 7 which employs not more than 0.013 mg/kg, not more than 0.01 mg/kg, 0.0085 mg/kg or 0.007 mg/kg~~.~~, and/or

~~12. A method, compound for use or use of a compound as claimed in any of claims 7 to 11~~ which employs more than 0.0014 mg/kg or 0.002 mg/kg.

~~13~~9. A ~~method,~~ compound for use or use of a compound as claimed in any of claims ~~7~~ 5 to ~~12~~ 8 which employs 0.0014 mg/kg to 0.0085 mg/kg or 0.002 mg/kg to 0.007 mg/kg.

~~14~~10. A ~~method,~~ compound for use or use of a compound as claimed in any of claims ~~7~~ 5 to ~~13~~ 9 which employs tacrolimus.

~~15. A method of treating a disease characterised by protein aggregate deposition in a neuronal cell which comprises administering to a human in need thereof by administration not more than once a day of an effective amount of tacrolimus or a close structural analogue to effect epigenetic modification which leads to an enhancement of autophagy and/or reduction in oxidative stress.~~

~~16~~11. Tacrolimus or a close structural analogue thereof for use in the treatment of a disease characterised by protein aggregate deposition by administration not more than once a day of an amount which effects epigenetic modification which leads to an increase in autophagy and/or an improvement in oxidative stress.

~~17~~12. The use of tacrolimus or close structural analogue thereof in the manufacture of a medicament for the treatment of a disease characterised by protein aggregate deposition in neuronal cells by administration not more than once per day which medicament contains an amount of tacrolimus or close structural analogue thereof which effects epigenetic modification which leads to an increase in autophagy and/or an improvement in oxidative stress.

~~18~~13. A ~~method,~~ compound for use or use of a compound as claimed in ~~any of~~ claim~~s~~ 11 or 12 ~~15 to 17~~ which employs tacrolimus.

~~19~~14. A unit dose pharmaceutical composition containing 0.05 mg to 1.3 mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier therefor for use in the treatment of a disease characterised by protein aggregate deposition in neuronal cells.

~~20~~15. A unit dose pharmaceutical composition as claimed in claim ~~19~~ 14 which does not contain more than 1.2 mg, 0.75 mg, 0.6 mg or 0.4 mg of tacrolimus or a close structural analogue thereof~~.~~, and/or

~~21. A unit dose pharmaceutical composition as claimed in claims 19 or 20~~ which comprises not less than 0.06, 0.1 or 0.15 mg.

~~22~~16. A unit dose pharmaceutical composition as claimed in ~~any of~~ claim~~s~~ 14 or 15 ~~19 to 21~~ adapted for administration by mouth.

~~23~~17. A ~~method,~~ compound or pharmaceutical composition for use, use of a compound or pharmaceutical composition as claimed in any of claims 1 to ~~22~~ 16 for use where the disease is amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, sycleinopathy or taupathy.

~~24. A method, compound or pharmaceutical composition for use, or use of a compound or pharmaceutical composition as claimed in any of claims 1 to 22, wherein the disease is Alzheimer's disease.~~

~~25. A method, compound or pharmaceutical composition for use, or a use of a compound or pharmaceutical composition as claimed in any of claims 1 to 22, wherein the disease is Parkinson's disease.~~

~~26. A method, compound or pharmaceutical composition for use, or a use of a compound or pharmaceutical composition as claimed in any of claims 1 to 22, wherein the disease is Huntingdon's disease.~~

~~27. A method, compound or pharmaceutical composition for use, or a use of a compound or pharmaceutical composition as claimed in any of claims 1 to 22, wherein the disease is a cycleinopathy or taupathy.~~

~~28~~18. A ~~method,~~ compound or pharmaceutical composition for use, or use of a compound or pharmaceutical composition as claimed in claim ~~27~~17, which is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementia's and memory loss conditions associated with eye related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~29~~19. A ~~method,~~ compound for use or pharmaceutical composition for use, or use of a compound or pharmaceutical composition as claimed in ~~any of~~ claims 17 or 18 ~~23 to 28~~ which employs tacrolimus.

~~30~~20. A unit dose orally administrable pharmaceutical composition comprising 0.05 mg to 1.2 mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier for use in the treatment of a disease characterised by the deposition of protein aggregates in neuronal cells.

~~31~~21. A unit dose for use as claimed in claim ~~30~~ 20 wherein the disease is ALS, Parkinson's disease, Alzheimer's disease, Huntingdon's disease.

~~32~~22. A unit dose for use as claimed in claims ~~30~~ 20 or ~~31~~ 21 which comprises tacrolimus.

~~33~~23. A unit dose for use as claimed in claims ~~30~~ 20 to ~~32~~ 22 which comprises not more than 0.9 mg, 0.75 mg, 0.65 mg or not more than 0.5 mg or not more than 0.45 mg of tacrolimus.

~~34~~24. A unit dose for use as claimed in any of claims ~~30~~ 20 to ~~33~~ 23 which comprises not less than 0.05 mg, not less than 0.1 mg or not less than 0.15 mg of tacrolimus or close structural analogue thereof.

~~35~~25. A unit dose for use as claimed in any of claims ~~30~~ 20 to ~~34~~ 24 in the form of a tablet or capsule.

~~36. A method of treatment of a disease characterised by the deposition of protein aggregate in neural cells which comprises administering to a patient in need thereof a pharmaceutical composition by oral administration which comprises an amount of tacrolimus or close structural analogue thereof as set forth in any of claims 30 to 35.~~

~~37. A method as claimed in claim 36 wherein tacrolimus is administered not more than once per day.~~