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

~~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~~ one 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 in a human 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~~ does not cause immunosuppression and which has a trough whole blood level of at least 0.05 ng/mL,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl

group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~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 in a human 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,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~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~~ a further 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 in a human 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,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

In another ~~a further~~ aspect of the present disclosure, there is provided a use of 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, in the manufacture of a medicament for ~~use in~~ the treatment of a disease in a human characterised by protein aggregate deposition in neuronal cells,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

In ~~another~~ a further aspect of the present disclosure, there is provided a use of a unit dose orally administrable pharmaceutical composition comprising 0.05 mg to 1.3~~1.2~~ mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier, in the manufacture of a medicament for ~~use in~~ the treatment of a disease in a human characterised by the deposition of protein aggregates in neuronal cells,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

The present 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.

indicated an oral dose of 0.22-0.16 mg/day for a 70 kg person with a blood level of 1-0.4 mg/mL as particularly effective.

In a further aspect the present invention provides a unit dose pharmaceutical composition containing 0.05 mg to 1.2 mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier therefore for use in the treatment of a disease characterized by deposition of protein aggregates in neuronal cells.

Suitably the disease may be ALS. Suitably the disease may be Parkinson's disease. Suitably the disease may be Alzheimer's disease. Suitably the disease may be Huntingtdon's disease.

The unit dose may contain not more than 0.9 mg or 0.75 mg, for example a dose of not more than 0.65 mg such as not more than 0.5 mg or not more than 0.45 mg of tacrolimus or a close structural analogue thereof, preferably tacrolimus.

Such unit dose may be for administration as described herein, particularly for oral administration.

The unit dose may contain not less than 0.05 mg, favourably not less than 0.1 mg, for example not less than 0.15 mg of tacrolimus or a close structural analogue thereof, preferably tacrolimus.

Hence, aptly the unit dose may contain from 0.05 mg to 0.9 mg, for example from 0.1 mg to 0.75 mg, for example from 0.15 mg to 0.6 mg or from 0.15 mg to 0.5 or 0.45 mg

Claims

~~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.~~

~~2~~1. The use of tacrolimus or its close structural analogue in the manufacture of a medicament for the treatment of a disease in a human 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~~ does not cause immunosuppression and which has a trough whole blood level of at least 0.05 ng/mL,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~3~~2. The ~~A compound for use or~~ use ~~of a compound~~ as claimed in claim 1 ~~or 2~~ 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 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.

~~4~~3. The ~~A compound for use or~~ use ~~of a compound~~ as claimed in ~~any of~~ claim~~s~~ 1 or 2 ~~to 3~~ which employs tacrolimus.

~~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.~~

~~6~~4. The use of tacrolimus or a close structural analogue in the manufacture of a medicament for treating a disease in a human 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,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~7~~5. ~~The~~ A ~~compound for use or~~ use ~~of a compound~~ as claimed in claim ~~3 4 or 5~~ which employs 0.001 mg/kg to 0.02 mg/kg.

~~8~~6. ~~The~~ A ~~compound for use or~~ use ~~of a compound~~ as claimed in ~~any of~~ claim~~s~~ ~~4 or~~ 5 ~~to 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 which employs more than 0.0014 mg/kg or 0.002 mg/kg.

~~9~~7. ~~The~~ A ~~compound for use or~~ use ~~of a compound~~ as claimed in any of claims ~~4 to 6~~ 5 to 8 which employs 0.0014 mg/kg to 0.0085 mg/kg or 0.002 mg/kg to 0.007 mg/kg.

~~10~~8. ~~The~~ A ~~compound for use or~~ use ~~of a compound~~ as claimed in any of claims ~~4 to 7~~ 5 to 9 which employs tacrolimus.

~~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.~~

~~129~~. The use of tacrolimus or close structural analogue thereof in the manufacture of a medicament for the treatment of a disease in a human 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,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~1310~~. The ~~A compound for use or~~ use ~~of a compound~~ as claimed in claim ~~911 or 12~~ which employs tacrolimus.

~~1411~~. Use of a ~~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, in the manufacture of a medicament for ~~use in~~ the treatment of a disease in a human characterised by protein aggregate deposition in neuronal cells,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~15~~12. The use ~~A unit dose pharmaceutical composition~~ as claimed in claim 11~~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 which comprises not less than 0.06, 0.1 or 0.15 mg.

~~16~~13. The use ~~A unit dose pharmaceutical composition~~ as claimed in claim 11 or 12~~14 or 15~~, wherein said medicament is adapted for administration by mouth.

~~17~~14. The use ~~A compound or pharmaceutical composition for use, use of a compound or pharmaceutical composition~~ as claimed in any of claims 1 to 13~~16 for use~~ where the disease is amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntingdton's disease, synucleinopathy or tauopathy.

~~18~~15. The use ~~A compound or pharmaceutical composition for use, or use of a compound or pharmaceutical composition~~ as claimed in claim ~~17~~14, which is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with ~~eye~~ age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~19~~16. The use ~~A compound for use or pharmaceutical composition for use, or use of a compound or pharmaceutical composition~~ as claimed in claim 14 or 15~~17 or 18~~ which employs tacrolimus.

~~20~~17. Use of a~~A~~ unit dose orally administrable pharmaceutical composition comprising 0.05 mg to 1.3~~1.2~~ mg of tacrolimus or a close structural analogue thereof and a pharmaceutically acceptable carrier, in the manufacture of a medicament for ~~use in~~ the treatment of a disease in a human characterised by the deposition of protein aggregates in neuronal cells,

wherein said close structural analogue of tacrolimus is a tacrolimus derivative in which one hydrogen atom at either of the C_{18} and C_{21} positions has been substituted by a C_{1-4} alkyl, C_{2-4} alkenyl, hydroxyl or methyoxyl group, or in which the C_{21} propenyl group has been replaced by a hydrogen atom, a C_{1-6} alkyl group, a fluoro C_{1-6} alkyl group, another C_{2-6} alkenyl group, a hydroxyl group or a methoxyl group, and

wherein the disease characterised by protein aggregate deposition in neuronal cells is selected from the group consisting of:

(i) amyotrophic lateral sclerosis;

(ii) Alzheimer's disease;

(iii) Parkinson's disease;

(iv) Huntington's disease; or

(v) a synucleinopathy or tauopathy, wherein the synucleinopathy or tauopathy is a dementia, such as Parkinson's disease dementia and frontotemporal lobe dementia, or other dementias and memory loss conditions associated with age related increase of neurotoxic protein aggregation and/or increased oxidative stress or to defect in autophagy.

~~21~~18. The ~~A unit dose for~~ use as claimed in claim ~~20~~17 wherein the disease is ALS, Parkinson's disease, Alzheimer's disease, Huntingtdon's disease.

~~22~~19. The use ~~A unit dose for use~~ as claimed in claims 17 or 18~~20 or 21~~, wherein the unit dose ~~which~~ comprises tacrolimus.

2320. The A unit dose for use as claimed in claims 17 to 1920 to 22, wherein the unit dose 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.

2421. The A unit dose for use as claimed in any of claims 17 to 20 to 23, wherein the unit dose 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.

2522. The A unit dose for use as claimed in any of claims 17 to 2120 to 24, wherein the unit dose is in the form of a tablet or capsule.