relief from pain and muscle spasms, functional improvement in both active and passive dimensions, avoiding progression of impairment, and improving aesthetic and postural appearance. There may be little opportunity to restore active function, but improving the ease of caring for the affected limb, for example, in washing and dressing, can nevertheless have a significant impact on caregiver burden, and can potentially have significant cost benefits in terms of reducing the time taken, or the number of people required, to perform care tasks. BoNTA injections are recommended as a safe and effective treatment for the reduction of muscle spasticity and improvement of passive function in patients with ULS. Botulinum toxin injections are currently the first-line pharmacological option for treatment of focal ULS.

[0004] Botulinum toxin can help block the communication between the nerve and the muscle and may alleviate abnormal movements and postures. The number of injections is typically based on the severity of the spasticity. Doctors injecting the toxin may select the muscles to be injected by observing abnormal bending at joints or movements and feeling for the muscle spasm or by using electromyography (EMG) to measure muscle activity. Each muscle affected by spasticity typically has to be injected separately. As such, based on the diffusion characteristics of currently available toxin formulations, there is a limit to the total quantity of toxin that can be injected into the body at one time. While the treatment for ULS involves regular neurological intervention, which takes effect over a period of 4-7 days or longer after injection, the response to the treatment with botulinum toxin typically wears off after a 12 week period, often as early as at 10 weeks, requiring the person suffering from ULS to be injected again. Therefore, a durable, longer acting treatment requiring fewer neurological interventions would be desirable.

SUMMARY ~~OF THE INVENTION~~

[0005] In one of its ~~aspects~~examples, the ~~invention~~ disclosure relates to a method for producing a biologic effect in the treatment of ULS by injecting an effective amount, preferably a therapeutically effective amount, of the compositions of this ~~invention~~ disclosure to a subject or patient in need of such treatment. Such biologic effect can last for at least 16 weeks or longer extending the tme between subsequent treatments.

[0005a] In an aspect, there is provided the use of a treatment dose of a sterile injectable composition comprising a botulinum toxin component having a specific activity in the manufacture of a medicament for the treatment of upper limb spasticity in an individual, wherein the composition is to be administered by injection into one or more muscles contributing to the upper limb spasticity in the individual in need of treatment to achieve the therapeutic effect;

wherein the composition comprises a pharmaceutically acceptable diluent suitable for injection and the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the total treatment dose of botulinum toxin component to be administered to the individual is between 250 U to 1000 U;

wherein the composition comprises a positively charged carrier component comprising a positively charged backbone having covalently attached thereto one or more positively charged efficiency groups;

wherein the duration of treatment effect is at least 16 weeks.

[0006] An ~~embodiment~~ example of the disclosure comprises a method of treating ULS in an individual in need thereof by administering to the individual an injection of a composition

comprising: a botulinum toxin component and a positively charged carrier; and a pharmaceutically acceptable diluent for injection; wherein the botulinum toxin is administered to the individual in an amount from about 250 U to about 1000 U; wherein the positively charged carrier is non-covalently associated with the botulinum toxin component; and wherein injection of the composition provides a treatment having at least about a four month to about a 9 months duration of effect in reducing the symptoms of ULS, thereby extending treatment interval duration for the individual. In embodments, the positively charged carrier can be a positively charged polylysine backbone having covalently attached thereto one or more positively charged efficiency groups having an amino acid sequence of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO: 1), (gly)p- Y GRKKRRQRRR-(gly)q (SEQ ID NO: 2) or (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20

[0007] In another of its ~~aspects~~examples, this ~~invention~~ disclosure provides injectable compositions comprising botulinum toxin non-covalently associated with a positively charged carrier molecule used to treat ULS. In preferred ~~embodiments~~examples, the compositions of the ~~invention~~ disclosure possess one or more advantages over conventional commercial botulinum toxin formulations, such as BOTOX® or MYOBLOC®. For instance, in certain ~~embodiments~~examples, the compositions may exhibit one or more advantages over conventional injectable botulinum formulations, including reduced antigenicity, a reduced tendency to undergo diffusion into surrounding tissue following injection, increased duration of clinical efficacy or enhanced potency relative to conventional botulinum toxin formulations, faster onset of clinical efficacy, and/or improved stability.

[0008] While not wishing to be bound by theory, the positively charged carriers are non-native molecules (i.e., molecules not found in botulinum toxin complexes obtained from Clostridium botulinum bacteria) that can improve toxin diffusion through tissues in the treatment of ULS. The positively charged carriers can associate non-covalently with the toxin and are believed to act as penetration enhancers that improve the ability of the toxin to reach target structures after injection. Furthermore, the positively charged carriers may increase the stability of the toxin prior to and after injection. By way of example, the The positively charged carriers can be cationic peptides, which have no inherent botulinum-toxin-like activity and which also contain one or more protein transduction domains as described herein.

[0009] The compositions comprising botulinum toxin component can be the 150 kD neurotoxin itself, or the neurotoxin with some, but not all, of the native complex proteins).

[0010] Methods of the present dislcosure provide effective doses and amounts of the compositions of this ~~invention~~ disclosure in the treatment of ULS that afford a long-lasting, sustained efficacy following administration by injection to a subject or patient in need of treatment. Such doses and amounts are preferably therapeutically effective doses and amounts that produce or result in a desired therapeutic effect in a subject to whom the doses and amounts are administered. In particular ~~embodiments~~examples, a single treatment of a subject or patient with a composition of the ~~invention~~ disclosure comprising a botulinum toxin, such as botulinum toxin A, and a positively charged carrier, as described herein, in therapeutically effective dose amounts of about 250 U to about 500 U per subject, afford a response rate in the reduction of ULS symptoms for at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks.

[0011] The duration of effect provided by compositions described herein as well as by the described treatment methods and uses, affords significant advantages compared to the art. By way of example, subjects undergoing treatment with compositions containing botulinum toxin benefit from having a duration of effect following treatment to be of that reduces the need for follow up or repeat treatment, or extends the interval between treatments. Such a long, sustained duration of effect, which is achieved by even a single treatment with an effective dose and treatment regime of a product of the ~~invention~~disclosure, for example, DAXI described in Example 1, permits fewer injections per treatment course for a subject. A prolonged duration effect from a single treatment with a product which has clear efficacy and safety, as provided by the inventive compositions and methods described herein, offer less discomfort, less cost as result of few treaments, and more convenience to subjects undergoing a course of treatment. Furthermore, a product that affords significant and sustained effects, which are maintained for at least a 16, 20, 24, 28, 32, or 36 week period following the single treatment of the product to a subject, provides a solution to an unmet need in the art for both practitioners and patients alike. Thus, the compositions and methods of the ~~invention~~disclosure provide a solution to the problem of too frequent treatments and improve patients' overall well-being. Such prolonged duration of action provides for fewer treatments over an entire treatment course.

[0012] The disclosure described herein is directed to a method of administering botulinum toxin to achieve an extended duration therapeutic effect in an individual suffering from ULS, in which the method comprises administering by injection a dose of a sterile injectable composition into an area of the individual in need of treatment to achieve the therapeutic effect following a first treatment with the composition; wherein the composition comprises a botulinum toxin component and a positively charged carrier ; wherein the botulinum toxin component is administered to the individual in a treatment dose of about 250 U to 1000 U; or more specifically, from about 250 U to 500 U or from about 500 U to 700 U or from about 600 U to 800 U or from about 800 U to 1000 U, wherein the positively charged carrier is non-covalently associated with the botulinum toxin, botulinum toxin complex, or reduced botulinum toxin complex component; and a pharmaceutically acceptable diluent suitable for injection; and wherein the first treatment dose of the composition administered by injection to the individual achieves the extended duration therapeutic effect of at least 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, or 36 weeks before a second or subsequent treatment dose is administered. In ~~embodiments~~examples, the positively charged carrier can comprise a positively charged polylysine backbone having covalently attached thereto one or more positively charged efficiency groups having an amino acid sequence of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO: 1), (gly)p-Y GRKKRRQRRR-(gly)q (SEQ ID NO: 2) or (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20

[0013] The disclosure described herein is directed to a sterile injectable composition for treating one or more types (e.g., clinical presentation patterns) of ULS comprising a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex in a dosage amount selected from more than 250 U, from 250 U to 500 U, 500-750 U, or 750-1000 U; and a positively charged carrier comprising a positively charged polylysine backbone having covalently attached thereto one or more positively charged efficiency groups having an amino acid sequence of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO: 1), (gly)p- Y GRKKRRQRRR-(gly)q (SEQ ID NO: 2) or (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20; and a pharmaceutically acceptable diluent for injection; wherein the positively charged carrier is non-covalently associated with the botulinum toxin, botulinum toxin complex, or reduced botulinum toxin complex component; and wherein the composition provides a therapeutic effect that endures for at least 16 to 24 or 16 to

36 weeks following a treatment of an individual with an effective dose of the injectable composition.

[0014] In some ~~embodiments~~ examples of these above methods and composition, the composition comprises botulinum toxin of serotype A, preferably a serotype A botulinum toxin having a molecular weight of 150 kDa. In an ~~embodiment~~example, the positively charged carrier has the amino acid sequence RKKRRQRRRG-(K) $_{15}$ -GRKKRRQRRR (SEQ ID NO: 4). In an ~~embodiment~~example, and specifically including RKKRRQRRRG-(K) $_{15}$ - GRKKRRQRRR (SEQ ID NO: 4), the botulinum toxin, specifically including the 150 kDa botulinum toxin A, is present in the composition in a dosage amount from more than 250 U to 500 U, 500-750 U, or 750-1000 U. In an example~~embodiment~~, the botulinum toxin is present in the composition in a dosage amount selected from the group consisting of 250 U, 375 U, 500U, 600 U, 700 U, 800 U, 900 U, and 1000 U. In an ~~embodiment~~example, the composition reduces the symptoms of ULS in an individual who has undergone a single treatment by injection of the composition. In certain ~~embodiments~~examples, the duration of the treatment effect is at leastl6 weeks, 20 weeks, 24 weeks.

[0015] In another of its ~~aspects~~examples, the ~~invention~~ disclosure provides a method of treating an individual suffering from one or more types of ULS who is in need of treatment with injectable botulinum toxin, in which the method of treatment comprises at least one treatment course, but may encompass a treatment course having multiple treatment treatments separated by treatment intervals with prolonged duration of effect and duration time between each treatment interval, the treatment course comprising: administering by injection an initial treatment dose of a sterile injectable composition into an area of the individual in need of treatment to achieve a therapeutic effect following the initial treatment with the composition; wherein the composition comprises a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex component and a positively charged carrier component comprising a positively charged polylysine backbone having covalently attached thereto one or more positively charged efficiency groups having an amino acid sequence of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO: 1), (gly)p-Y GRKKRRQRRR-(gly)q (SEQ ID NO: 2) or (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20; and a pharmaceutically acceptable diluent suitable for injection; wherein the botulinum toxin, botulinum toxin complex, or reduced botulinum toxin complex component is administered to the individual in a treatment dose of from more than 250 U, 250 U to 500 U, 500-750 U, or 750-

1000 U, wherein the positively charged carrier is non-covalently associated with the botulinum toxin, botulinum toxin complex, or reduced botulinum toxin complex component; wherein the initial treatment dose of the composition administered by injection to the individual provides a therapeutic duration of effect lasting through at least about 16 months to at least about 24 weeks; and administering subsequent treatment doses of the composition by injection to the individual at treatment intervals comprising a duration of greater than or equal to 16 weeks to at least about 24 weeks following the initial treatment dose and between each subsequent treatment dose. Such an ~~embodiment~~ example specifically contemplates the 150 kDa botulinum toxin type A with using the positively charged carrier RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4.

DESCRIPTION OF THE FIGURES

[0016] Fig. 1 illustrates the various types of ULS.

[0017] Fig. 2 shows the change from baseline in suprahypertonic muscle group modified Ashworth score (MAS) and physician global impression of change (PGIC) at week 6.

[0018] Fig. 3 shows the mean change from baseline on suprahypertonic muscle group (SMG) modified Ashworth score (MAS) over time.

[0019] Fig. 4 shows the change in modified Ashworth score (MAS) at week 6 for suprahypertonic muscle group (SMG), wrist, fingers and elbow.

[0020] Fig. 5 shows suprahypertonic muscle group (SMG) selection by treatment group.

[0021] Fig. 6 shows the mean change from baseline on modified Ashworth score (MAS) over time for wrist.

[0022] Fig. 7 shows the mean change from baseline on modified Ashworth score (MAS) over time for fingers.

[0023] Fig. 8 shows the mean change from baseline on modified Ashworth score (MAS) over time for fingers.

[0024] Fig. 9 shows the time to loss of improvement in suprahypertonic muscle group (SMG) (modified Ashworth score (MAS) change from baseline < 1 point) and physician global impression of change (PGIC) < or requesting retreatment.

Claims:

1. Use of ~~A method of treating upper limb spasticity in an individual, the method comprising:~~

~~administering by injection~~ a treatment dose of a sterile injectable composition comprising a botulinum toxin component having a specific activity in the manufacture of a medicament for the treatment of upper limb spasticity in an individual, wherein the composition is to be administered by injection into one or more muscles contributing to the upper limb spasticity in the individual in need of treatment to achieve the therapeutic effect;

wherein the composition comprises a pharmaceutically acceptable diluent suitable for injection and the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the total treatment dose of botulinum toxin component to be administered to the individual is between 250 U to 1000 U;

wherein the composition comprises a positively charged carrier component comprising a positively charged backbone having covalently attached thereto one or more positively charged efficiency groups;

wherein the duration of treatment effect is at least 16 weeks.

2. The ~~method~~ use of claim 1, wherein one or more types of upper limb spasticity are to be treated.

3. The ~~method~~ use of claim 2, wherein the one or more types of upper limb spasticity is selected from a clenched fist, flexed fingers, flexed elbow, flexed wrist, adducted and internally rotated shoulder, and pronated forearm.

4. The ~~method~~ use according to claim 3, wherein the individual presents with the one or more types of upper limb spasticity types, selected from a group consisting of flexed elbow, flexed wrist, and a clenched fist or flexed elbow, flexed wrist, and flexed fingers.

5. The ~~method~~ use according to any one of claims 2 to 4, wherein the treatment dose for clenched fingers comprises 50 to 100 U.

6. The ~~method~~use according to any one of claims 2 to 5, wherein the treatment dose for flexed wrist comprises 50 to 100 U.

7. The ~~method~~ use according to any one of claims 2 to 6, wherein the treatment dose for flexed elbow comprises 150 U to 400 U.

8. The ~~method~~use according to any one of clams 2 to 7, wherein the one or more muscles injected for treatment of flexed elbow comprise of biceps; brachioradialis; and brachialis.

9. The use~~method~~ according to any one of clams 2 to 8, wherein the one or more muscles injected for treatment of flexed wrist comprise or consist of flexor carpi radialis and flexor carpi ulnaris.

10. The use~~method~~ according to any one of clams 2 to 9, wherein the one or more muscles injected for treatment of clenched fingers comprise of flexor digitorum superficialis and flexor digitorum profundus.

11. The use~~method~~ according to any one of claims 2 to 10, wherein the individual presents with the one or more types of upper limb spasticity comprising adducted and internally rotated shoulder, pronated forearm, and thumb-in-palm.

12. The use~~method~~ according to any one of claims 2 to 11, wherein the treatment dose for adducted and internally rotated shoulder comprises 100 U to 400 U.

13. The use~~method~~ according to any one of claims 2 to 12, wherein the treatment dose for pronated forearm comprises 50 U to 300 U.

14. The use~~method~~ according to any one of claims 2 to 13, wherein the treatment dose for thumb-in-palm comprises 25 U to 150 U.

15. The use~~method~~ according to any one of clams 2 to 14, wherein the one or more muscles to be injected for treatment of adducted and internally rotated shoulder comprise pectoralis complex and latissimus dorsi.

16. The use~~method~~ according to any one of clams 2 to 15, wherein the one or more muscles to be injected for treatment of pronated forearm comprise pronator quadratus and pronator teres.

17. The use~~method~~ according to any one of clams 2 to 16, wherein the one or more muscles to be injected for treatment of thumb-in-palm comprise flexor pollicis longus, adductor pollicis; flexor pollicis brevis/opponens, and first interosseous.

18. The use~~method~~ according to any one of the preceding claims, wherein the risk of adverse events is less than 12%, 10%, 8%, 7%, 5%, or 3%.

19. The use~~method~~ of any one of the preceding claims, wherein the positively charged backbone comprises polylysine having covalently attached thereto one or more positively charged efficiency groups having an amino acid sequence selected from $(gly)_p$- RGRDDRRQRRR-$(gly)_q$ (SEQ ID NO: 1), $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO: 2) or $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20;

20. The use~~method~~ of claim 19, wherein (i) the subscripts p and q are each independently an integer of from 0 to 8; or (ii) are each independently an integer of from 2 to 5.

21. The use~~method~~ of claims 19 or 20, wherein the one or more positively charged efficiency groups are attached to either end, or both ends, of the positively charged polylysine backbone of the positively charged carrier.

22. The use~~method~~ of claim 19, wherein the positively charged carrier has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4) or RRRQRRKKRG- $(K)_{15}$-GRRRQRRKKR.

23. The use~~method~~ according to any one of the preceding claims, wherein the composition comprises botulinum toxin of serotype A.

24. The use~~method~~ according to any one of the preceding claims, wherein the composition comprises botulinum toxin of serotype A having a molecular weight of 150 kDa.

25. The use~~method~~ according to any one of the preceding claims, wherein the total treatment dose of botulinum toxin is to be administered to the individual in an amount that does not exceed 500 U, 600 U, 700 U, 800 U, 900 U, or 1000 U.

26. The use~~method~~ according to any one of the preceding claims, wherein a total treatment dose of botulinum toxin is to be administered to the individual in an amount of at least 200 U, 300 U, 400 U, 500 U, or 600 U.

27. The use~~method~~ according to any one of the preceding claims, wherein the duration of treatment effect comprises greater than 4 months or 16 weeks.

28. The use~~method~~ according to any any one of the preceding claims, wherein the duration of treatment effect comprises greater than 5 months or 20 weeks.

29. The use~~method~~ according to any one of any one of the preceding claims, wherein the duration of treatment effect comprises greater than 6 months or 24 weeks.

30. The use~~method~~ according to any one of the preceding claims, wherein the duration of treatment effect comprises at least 18 weeks.

31. The use~~method~~ according to any one of the preceding claims, wherein the duration of treatment effect comprises at least 22 weeks.

32. The use~~method~~ according to any one of of the preceding claims, wherein the duration of treatment effect comprises at least 26 weeks

33. The use~~method~~ according to any one of the preceding claims, wherein the composition is animal protein free or albumin-free.

34. The use~~method~~ according to any one of the preceding claims, wherein the risk of muscular weakness from the treatment is less than 8%, 7%, 6%, 5%, 4%, or 3%.

35. The use~~method~~ according to any one of the preceding claims, wherein the composition comprises a 150 kD botulinum toxin of serotype A, the positively charged carrier (optionally the peptide of SEQ ID NO: 4), a non-reducing disaccharide or a non-reducing trisaccharide selected from sucrose, trehalose and raffinose, a non-ionic surfactant selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and a sorbitan ester, and a physiologically compatible buffer secected from citric acid, acetic acid, succinic acid, tartaric acid, maleic acid, and histidine for maintaining the pH between 4.5 and 7.5.

36. The use~~method~~ according to any one of the preceding claims, wherein the composition comprises a 150 kD botulinum toxin of serotype A, the positively charged carrier (optionally the peptide of SEQ ID NO: 4), a non-reducing disaccharide or a non-reducing trisaccharide selected from trehalose, polysorbate 20, and histidine buffered to a pH between 4.5 and 7.5.