METHODS FOR TREATING TYPE 1 DIABETES

RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/192,402, filed May 24, 2021, and U.S. Utility Patent Application No. 17/752,660, filed May 24, 2022, the entire disclosures of each of which are incorporated herein by reference.

SEQUENCE LISTING

[0002] This specification includes a sequence listing submitted herewith, which includes the file entitled 178833-011101_ST25.txt having the following size: 6,058 bytes which was created May 23, 2022, the contents of which are incorporated by reference herein.

FIELD

[0003] The present disclosure relates in general to methods and dosage regimen for treating type 1 diabetes (T1D) in subjects in need thereof.

BACKGROUND

[0004] Type 1 diabetes (T1D) is caused by the autoimmune destruction of insulin producing beta cells in the islets of Langerhans leading to dependence on exogeneous insulin injections for survival. Approximately 1.6 million Americans have Type 1 diabetes, and after asthma, it remains one of the most common diseases of childhood. Despite improvements in care, most affected individuals with T1D are not able to consistently achieve desired glycemic targets. For individuals with type 1 diabetes, there are persisting concerns for increased risk of both morbidity and mortality. Two recent studies noted loss of 17.7 life-years for children diagnosed before age 10, and 11 and 13 life-years lost for adult-diagnosed Scottish men and women respectively.

[0005] Thus, a need exists for improved T1D treatment methods and compositions.

SUMMARY

[0006] In one aspect, the present disclosure pertains to a use of teplizumab in the manufacture of a medicament for treating type 1 diabetes (T1D), wherein the treatment comprises a 12-day course of teplizumab to be administered to a subject in need thereof at a total dose of from 9000 $\mu g/m^2$ to 9500 $\mu g/m^2$. In another aspect, the present disclosure pertains to a use of teplizumab in the manufacture of a medicament for treating type 1 diabetes (T1D), wherein the treatment comprises a 12-day course of teplizumab to be administered to a subject in need thereof at a total dose of from 9000 $\mu g/m^2$ to 14000 $\mu g/m^2$. Some examples relate to a method of

treating clinical type 1 diabetes (T1D), comprising administering to a subject in need thereof a 12-day course of teplizumab at a total dose of more than about 9000 μg/m^2. Some examples relate to teplizumab for use in a method of treating clinical type 1 diabetes (T1D), comprising administering to a subject in need thereof a 12-day course of the teplizumab at a total dose of more than about 9000 μg/m^2.

[0007] In some examples, the total dose is between about 9000 and about 9500 μg/m^2. In some examples, the total dose is between about 9000 and about 14000 μg/m^2.

[0008] In some examples, a method of treating type 1 diabetes (T1D) is provided comprising administering to a subject in need thereof a 12-day course of teplizumab at a total dose of from about 9000 to about 9500 μg/m^2. In some examples, a method of treating type 1 diabetes (T1D) is provided comprising administering to a subject in need thereof a 12-day course of teplizumab at a total dose of from about 9000 to about 14000 μg/m^2.

[0009] In some examples, the 12-day course comprises a first dose of 106 μg/m^2 teplizumab on day 1, a second dose of 425 μg/m^2 teplizumab on day 2, and one dose of 850 μg/m^2 on each of days 3–12, and wherein the total dose is approximately 9031 μg/m^2.

[0010] In some examples, the 12-day course comprises a first dose of 211 μg/m^2 teplizumab on day 1, a second dose of 423 μg/m^2 teplizumab on day 2, and one dose of 840 μg/m^2 on each of days 3–12, and wherein the total dose is approximately 9034 μg/m^2.

[0011] In some examples, the method can include administering a first and a second 12-day courses of teplizumab. In some examples, the first and the second 12-day courses are administered at about 1-6 months, about 2-5 months or about 3 months interval.

[0012] In some examples, the method can include administering to the subject in need thereof a third or more 12-day course of teplizumab, each course at a total dose of more than about 9000 μg/m^2.

[0013] In some examples, the third or more 12-day course of teplizumab comprises a first dose of 106 μg/m^2 teplizumab on day 1, a second dose of 425 μg/m^2 teplizumab on day 2, and one dose of 850 μg/m^2 on each of days 3–12, and wherein the total dose of each course is approximately 9031 μg/m^2.

[0014] In some examples, the third or more 12-day course of teplizumab comprises a first dose of 211 μg/m^2 teplizumab on day 1, a second dose of 423 μg/m^2 teplizumab on day 2, and one dose of 840 μg/m^2 on each of days 3–12, and wherein the total dose of each course is approximately 9034 μg/m^2.

[0015] In some examples, the third or more 12-day course of teplizumab is administered at about a 12 month to about a 24-month interval.

[0016] In some examples, the method can further include determining, after the administration of each 12-day course, a baseline of a level of TIGIT+KLRG1+CD8+ cells with respect to all CD3+ T cells, monitoring the level of the TIGIT+KLRG1+CD8+CD3+ T-cells and administering an additional 12-day course of teplizumab when the level of the TIGIT+KLRG1+CD8+CD3+ T-cells returns to the baseline level. In some examples, the determining of TIGIT+KLRG1+CD8+CD3+ T-cells is by flow cytometry. In some

examples, the monitoring of TIGIT+KLRG1+CD8+CD3+ T-cells is by flow cytometry. In some examples, the determining of TIGIT+KLRG1+CD8+CD3+ T-cells is about 1-6 months, about 2-5 months, or about 3 months after the administration of each 12-day course. In some examples, if the subject has more than about 10% TIGIT+KLRG1+CD8+ T-cells in all CD3+ T cells, subsequent monitoring is annual. In some examples, if the subject has less than about 10% TIGIT+KLRG1+CD8+ T-cells in all CD8+ T cells, subsequent monitoring is every about 3-6 months.

[0017] In some examples, the subject in need thereof has been diagnosed with T1D within 6 weeks prior to the administrating step.

[0018] In some examples, the administrating step results in reduction by at least 10% of insulin use, HbA1c levels, hypoglycemic episodes, or combinations thereof as compared to pre-treatment levels.

[0019] In some examples, each dose is administered parenterally.

[0020] In some examples, each dose is administered by intravenous infusion.

[0021] In some examples, the subject in need thereof is about 8 to 17 years old.

[0022] In some examples, the subject in need thereof have a peak C-peptide level of ≥0.2 pmol/mL during a mixed meal tolerance test (MMTT).

[0023] In some examples, the subject receiving teplizumab has a higher mean C-peptide value compared with a control receiving placebo.

[0024] In some examples, the method further includes assessing the area under the time-concentration curve (AUC) of C-peptide following a mixed meal tolerance test (MMTT), at 78 weeks.

[0025] In some examples, the subject in need thereof has at least 20% of beta-cell function prior the administration of the first dose.

[0026] In some examples, the reduction of insulin use, HbA1c levels, hypoglycemic episodes, or combinations thereof is over a period of 12 months or more.

[0026a] In another aspect, the present disclosure pertains to a use of teplizumab in the manufacture of a medicament for treating new-onset type 1 diabetes (T1D), wherein the treatment comprises two 12-day courses of teplizumab to be administered to a subject in need thereof at an interval of about 6 months, wherein each 12-day course comprises a first dose of about 106 μg/m^2 teplizumab on day 1, a second dose of about 425 μg/m^2 teplizumab on day 2, and one dose of about 850 μg/m^2 teplizumab on each of days 3–12.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Figure 1: Simulated Concentrations for Three Dosing Regimens: Population Predictions for a Typical Male Patient with WT = 60 kg, Age = 18 years, BSA=1.67 m^2, and no Detected ADAs.

[0028] Figure 2: Comparison of Concentrations for Dosing Regimens 1 and 2: Model-based Simulations for a Typical Male Patients with WT = 60 kg, Age = 18 years, BSA=1.67 m^2, and

CLAIMS

1. Use of teplizumab in the manufacture of a medicament for treating type 1 diabetes (T1D), wherein the treatment comprises a 12-day course of teplizumab to be administered to a subject in need thereof at a total dose of from 9000 μg/m^2 to 9500 μg/m^2.

2. Use of teplizumab in the manufacture of a medicament for treating type 1 diabetes (T1D), wherein the treatment comprises a 12-day course of teplizumab to be administered to a subject in need thereof at a total dose of from 9000 μg/m^2 to 14000 μg/m^2.

3. The use of claim 1 or 2, wherein the 12-day course comprises
a first dose of about 106 μg/m^2 teplizumab on day 1,
a second dose of about 425 μg/m^2 teplizumab on day 2, and
one dose of about 850 μg/m^2 teplizumab on each of days 3–12.

4. The use of claim 1 or 2, wherein the 12-day course comprises
a first dose of about 211 μg/m^2 teplizumab on day 1,
a second dose of about 423 μg/m^2 teplizumab on day 2, and
one dose of about 840 μg/m^2 teplizumab on each of days 3–12.

5. The use of any one of claims 1-4, wherein the treatment comprises two 12-day courses of teplizumab to be administered.

6. The use of claim 5, wherein the two courses are to be administered at an interval of about 6 months.

7. The use of claim 5 or 6, wherein the treatment further comprises additional one or more 12-day courses of teplizumab to be administered to the subject, with each additional course at a total teplizumab dose of from 9000 μg/m^2 to 9500 μg/m^2 or 14000 μg/m^2.

8. The use of claim 7, wherein each 12-day course of teplizumab comprises
a first dose of about 106 μg/m^2 teplizumab on day 1,
a second dose of about 425 μg/m^2 teplizumab on day 2, and
one dose of about 850 μg/m^2 teplizumab on each of days 3–12.

9. The use of claim 7, wherein each 12-day course of teplizumab comprises
a first dose of about 211 μg/m^2 teplizumab on day 1,
a second dose of about 423 μg/m^2 teplizumab on day 2, and
one dose of about 840 μg/m^2 teplizumab on each of days 3–12.

10. The use of claim 7, wherein each of the additional 12-day course of teplizumab is to be administered at 6 months to 24 months after the preceding course.

11. The use of any one of claims 1-10, wherein the treatment comprises determining, after administration of each 12-day course, a baseline of a level of TIGIT+KLRG1+CD8+ T-cells with respect to all CD3+ T-cells,

monitoring the level of the TIGIT+KLRG1+CD8+CD3+ T-cells, and

an additional 12-day course of teplizumab to be administered when the level of the TIGIT+KLRG1+CD8+CD3+ T-cells returns to the baseline level.

12. The use of claim 11, wherein the determining of TIGIT+KLRG1+CD8+CD3+ T-cells is by flow cytometry.

13. The use of claim 11, wherein the monitoring of TIGIT+KLRG1+CD8+CD3+ T-cells is by flow cytometry.

14. The use of claim 11, wherein the determining of TIGIT+KLRG1+CD8+CD3+ T-cells is 1-6 months, 2-5 months, or about 3 months after the administration of each 12-day course.

15. The use of claim 11, wherein if the subject has more than about 10% TIGIT+KLRG1+CD8+ T-cells in all CD3+ T-cells, subsequent monitoring is annual.

16. The use of claim 11, wherein if the subject has less than about 10% TIGIT+KLRG1+CD8+ T-cells in all CD3+ T-cells, subsequent monitoring is every 3-6 months.

17. The use of any one of claims 1-16, wherein the subject has been diagnosed with T1D within 6 weeks prior to administering the medicament.

18. The use of any one of claims 1-17, wherein the administration results in reduction of insulin use, HbA1c levels, hypoglycemic episodes, or combinations thereof by at least 10% as compared to pre-treatment levels.

19. The use of any one of claims 1-18, wherein each dose is to be administered parenterally.

20. The use of any one of claims 1-19, wherein each dose is to be administered by intravenous infusion.

21. The use of any one of claims 1-20, wherein the subject is 8 to 17 years old.

22. The use of any one of claims 1-21, wherein the subject has a peak C-peptide level of $\geq$0.2 pmol/mL during a mixed meal tolerance test (MMTT).

23. The use of any one of claims 1-21, wherein the subject receiving teplizumab has a higher mean C-peptide value compared with a control subject receiving placebo.

24. The use of any one of claims 1-23, wherein the treatment comprises assessing the area under the time-concentration curve (AUC) of C-peptide following a mixed meal tolerance test (MMTT) at 78 weeks.

25. The use of any one of claims 1-24, wherein the subject has at least 20% of beta-cell function prior to administration of the first dose.

26. The use of any one of claims 1-25, wherein reduction of insulin use, HbA1c levels, hypoglycemic episodes, or combinations thereof is over a period of 12 months or more.

27. Use of teplizumab in the manufacture of a medicament for treating new-onset type 1 diabetes (T1D), wherein the treatment comprises two 12-day courses of teplizumab to be administered to a subject in need thereof at an interval of about 6 months, wherein each 12-day course comprises

a first dose of about 106 μg/m^2 teplizumab on day 1,

a second dose of about 425 μg/m^2 teplizumab on day 2, and

one dose of about 850 μg/m^2 teplizumab on each of days 3–12.

28. The use of claim 27, wherein the treatment further comprises one or more additional 12-day courses of teplizumab to be administered to the subject.

29. The use of claim 28, wherein each of the additional 12-day courses of teplizumab comprises

a first dose of about 106 μg/m^2 teplizumab on day 1,

a second dose of about 425 μg/m^2 teplizumab on day 2, and

one dose of about 850 μg/m^2 teplizumab on each of days 3–12.

30. The use of claim 29, wherein each of the additional 12-day courses of teplizumab is to be administered at 6 months to 24 months after the preceding course.