3 and 4 (C3 and C4) and of anti-dsDNA. However, the criteria for normalization of C3, C4 and anti-dsDNA were not disclosed.

[0012] An earlier study with respect to lupus treatment with cyclophosphamide rather than Voclosporin suggested normalization of C4 as a marker. Dall'Era, M. et al Arth. Care and Res. (2011) 63:351-357.

[0013] It has now been found that successful results, including a diminution in the number and severity of side effects can be obtained by altering the protocols disclosed in these publications by providing a pharmacodynamic dosing schedule based on individual patient responses. In addition, it has been found that even lower dosages of voclosporin—*i.e.*, 15.8mg of voclosporin twice daily or 7.9mg of voclosporin twice daily are effective.

SUMMARY

[0014] The present disclosure, thus, provides an improved protocol for treatment of lupus nephritis and other proteinuric kidney diseases that takes advantage of assessments of parameters associated with the response of individual subjects. The disclosure is a personalized form of a protocol for treatment of proteinuric kidney diseases including protocols that employ low dosage of voclosporin. The voclosporin used is preferably a mixture of greater than about 80% E isomer and less than about 20% Z isomer, and more preferably greater than about 90% E isomer and less than about 10% Z isomer. The protocol employs daily dosages of voclosporin over a projected period of 24, 48, 52 weeks or longer wherein the voclosporin is administered twice daily (BID). Suitable dosages are in increments of 7.9 mg including 39.5 mg, 31.6 mg, 23.7 mg, 15.8 mg or 7.9 mg. Low dosages show superior results compared to a higher dose of 39.5 mg each of such administrations carried out twice daily. Doses as low as 15.8 mg or 7.9 mg twice daily are effective. The protocol preferably further includes administering to the subject an effective amount of MMF and/or an effective amount of a corticosteroid, typically prednisone, in a reducing dosage level across the time period of the study.

[0015] While it has been verified that the protocols of the disclosure are effective for lupus nephritis, such results indicate the same protocols can be used to generally treat proteinuric kidney diseases. Proteinuric kidney diseases that can be treated include: Diabetic nephropathy, nephrotic syndromes (i.e. intrinsic renal failure), nephritic syndromes, toxic lesions of kidneys, glomerular diseases, such as membranous glomerulonephritis, focal segmental glomerulosclerosis (FSGS), IgA nephropathy (i.e., Berger's disease), IgM

nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, hypertensive nephrosclerosis and interstitial nephritis.

[0016] One of the side effects of treatment with voclosporin is an unwanted decrease in the estimated glomerular filtration rate (eGFR). One disclosure protocol is designed to reduce the incidence of this undesirable side effect by adjusting the dosage in accordance with the response of the subject.

[0017] Thus, in one example, the disclosure is directed to a pharmacodynamic method to treat a proteinuric kidney disease which method comprises administering to a subject diagnosed with said disease a predetermined daily dosage of effective amounts of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:

(a) assessing the estimated Glomerular Filtration Rate (eGFR) of said subject at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the eGFR of said subject decreases by more than a target % to below a predetermined value between said first and second time points, reducing the daily dosage by increment(s) of 7.9mg BID or stopping the administering of voclosporin to said subject;

(ii) if the eGFR of said subject decreases by less than said target % between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0017a] In one aspect, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of a proteinuric kidney disease, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered to a subject diagnosed with said disease over a projected treatment period of at least 24 weeks, wherein:

(a) the estimated Glomerular Filtration Rate (eGFR) of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, both said time points occurring prior to the end of the treatment period and

(b) (i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73m^2 between said first and second time points, the daily dosage is to be reduced by increment(s) of 7.9mg BID or the administration of voclosporin to said subject is to be stopped;

(ii) if the eGFR of said subject decreases by less than said target % between said first and second time points, administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

[0017b] In another aspect, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of a proteinuric kidney disease, wherein predetermined daily dosages of effective amounts of voclosporin are to be administered to a subject diagnosed with a proteinuric kidney disease over a projected treatment period to an end point, wherein:

(a) urinary protein creatinine ratio (UPCR) of said subject is to be measured at a first time point prior to said treatment period and a second time point occurring prior to the end point but after the start of the treatment period and any reduction of said UPCR between said first and second time points is to be determined, and

(b) if the UPCR of said subject fails to show a reduction of at least a predetermined amount in the range of 15%-35% at said second time point, administration of voclosporin to the subject is to be discontinued and said administration is to be continued if said predetermined amount of reduction is shown.

[0018] In one specific example, the disclosure includes a pharmacodynamic method to treat lupus nephritis which method comprises administering to a subject diagnosed with lupus nephritis a predetermined daily dosage of effective amounts of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:

(a) assessing the glomerular filtration rate (eGFR) of said subject at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the eGFR of said subject decreases by $\geq$30% to a value of below 60 mL/min/1.73m^2 between said first and second time points, stopping the administering of voclosporin to said subject;

(ii) if the eGFR of said subject decreases by between 20% to 30% to a value of below 60 ml/min/1.73m^2 between said first and second time points, administering a reduced dosage of voclosporin to said subject;

(iii) if the eGFR of said subject decreases by $\leq$20% between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0019] The eGFR of 60 mL/min/1.73m^2 noted above is typically used; however, higher values such as 90 mL/min/1.73m^2 or 75 or 70 mL/min/1.73m^2 or lower value such as 50 mL/min/1.73m^2 or 55 mL/min/1.73m^2 could also be used.

[0020] The pharmacodynamic method may employ a third time point subsequent to the first and second time point wherein the target percentage reduction is again determined and if the percentage reduction as compared to the first time point is less than the target percentage, treatment may be restored, or if the percentage decrease is greater than the target percentage exhibited at the second time point, further reduction in dosage may be indicated.

[0021] A second example relates to using blood pressure as an indicator rather than eGFR. In this second example, the disclosure is directed to a pharmacodynamic method to treat lupus nephritis which method comprises administering to a subject diagnosed with lupus nephritis predetermined daily dosages of effective amounts of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:

(a) measuring the blood pressure (BP) of said subject at at least a first time point of said treatment period; and

(b) stopping the administering of voclosporin to the subject or administering a reduced dosage of voclosporin to said subject if either value of the cystolic or diastolic component of the BP of said subject is >130/80.

[0022] In this case, an additional time point measuring BP may be employed and if both components of the BP of the subject are below 130/80, the administration of the predetermined daily dose of voclosporin may be resumed.

[0023] Thus, blood measure elevation is an additional undesirable side-effect of treatment that can be used as a criterion for adjusting dosage.

[0024] It has also been found that the effectiveness of the protocol can be evaluated after only a portion of the treatment period has elapsed. This can be done in lieu of, or in addition to, the foregoing protocol. Therefore, because it is generally undesirable to continue an ineffective treatment an assessment at a time point earlier in the protocol than the end point planned is conducted and if the effectiveness of treatment is not confirmed, the treatment is

[0029] In addition, lowered levels of voclosporin dosage have been shown to be effective.

[0030] Thus, in another example, the disclosure is directed to a method to treat lupus nephritis which method comprises administering to a subject diagnosed with lupus nephritis a predetermined daily dosage of effective amounts of voclosporin wherein said effective amount is either 15.8mg BID or 7.9mg BID. Surprisingly, it has been found that these lower dosages are effective in a majority of patients, especially if the treatment is prolonged beyond 24 weeks. A dosage of 31.6 mg BID (4 capsules) could also be employed. Pharmacodynamic dosing can be applied in these instances as well.

[0030a] In another aspect, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for treating a proteinuric kidney disease, wherein a predetermined daily dosage of voclosporin is to be administered to a subject diagnosed with lupus nephritis over a protocol that consists of a projected treatment period of at least 8 weeks, wherein said the dosage of voclosporin is15.8/mg BID or 7.9/mg voclosporin BID and does not exceed 15.8 mg BID over the entire protocol and wherein said subject is to be administered voclosporin only in said protocol.

[0031] It is also advantageous and part of the disclosure to evaluate a subject who has been treated with the protocol at the end of the treatment period to determine whether a complete or partial remission has occurred. Further evaluations are included at a time subsequent to termination of the treatment to assess whether the remission achieved according to the measurement at the end of the treatment is being maintained. Such evaluation may also be done at intermediate times during treatment to determine whether dosage can be reduced. In an exemplary example used simply for illustration a dosage of 23.6 mg voclosporin BID may be reduced to 15.8 mg or 7.9 mg BID based on such results.

[0032] The evaluation for effectiveness can be based on the protein/creatinine ratio in urine (UPCR) where a ratio of ≤ 0.5 mg/mg indicates complete response; alternatively, or in addition, an eGFR of ≥ 60 mL/min/1.73m^2 or no decrease from baseline and eGFR of $\geq 20\%$ is shown. Other indications of complete response include lack of need for rescue medications such as intravenous steroids, cyclophosphamide or a need for ≤ 10 mg prednisone for more than three consecutive days or more than seven days total. These evaluations may be performed at any point in the treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Figure 1 shows graphically the design of a protocol for treatment of lupus nephritis with voclosporin upon which the pharmacodynamic treatment of the invention is superimposed.

[0034] Figure 2 is a bar graph showing a comparison of complete remission (CR) at 48 weeks and partial remission (PR) at 48 weeks for low dose as compared to high dose of voclosporin (VCS). The PR percentages include the CR percentages.

CLAIMS

1. Use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of a proteinuric kidney disease, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered to a subject diagnosed with said disease over a projected treatment period of at least 24 weeks, wherein:

(a) the estimated Glomerular Filtration Rate (eGFR) of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, both said time points occurring prior to the end of the treatment period and

(b) (i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73m^2 between said first and second time points, the daily dosage is to be reduced by increment(s) of 7.9mg BID or the administration of voclosporin to said subject is to be stopped;

(ii) if the eGFR of said subject decreases by less than said target % between said first and second time points, administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

2. The use of claim 1 wherein the first time point is immediately preceding initiating said protocol.

3. The use of claim 1 wherein the predetermined value is approximately 60ml/min/1.73m^2.

4. The use of claim 1 wherein the target % is approximately 30%.

5. The use of claim 1 wherein said subject as appropriate for said use is identified prior to said use on said subject by:

(a) determining that the urine protein creatinine ratio (UPCR) of said subject is $\geq$1mg/mg as measured by first morning void or 24 hour urine; and

(b) determining said subject has an eGFR as measured by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EP1) of $\geq$45 ml/min/1.73m^2,

wherein if the conditions of (a) and (b) are met, said subject is identified as appropriate for said use.

6. The use of any of claims 1-5 wherein said predetermined daily dosage is 39.5.mg voclosporin BID or 31.6mg voclosporin BID or 23.7mg voclosporin BID or 15.8mg voclosporin BID or 7.9mg voclosporin BID.

7. The use of any of claims 1-5 wherein said subject is to be evaluated for renal function at a time point after the end of said treatment period by assessing eGFR.

8. The use of claim 7 wherein said subject is to be evaluated for efficacy by assessing protein/creatinine ratio (UPCR) at a time point after the end of said treatment period.

9. The use of any of claims 1-5 wherein an effective amount of mycophenolate mofetil (MMF) is to be further administered to said subject.

10. The use of any of claims 1-5 wherein an effective amount of a corticosteroid is to be further administered to said subject.

11. The use of any of claims 1-5 wherein said treatment period is at least 48 weeks.

12. The use of any of claims 1-5 wherein the eGFR of said subject is to be determined at a third time point and if the eGFR is determined at said third time point to differ from the eGFR determined at said first time point by less than said target %, administration of said predetermined daily dosage of voclosporin in the range of 20-45% is to be resumed.

13. The use of claim 15 wherein the target % is approximately 30%.

14. Use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of a proteinuric kidney disease, wherein

predetermined daily dosages of effective amounts of voclosporin are to be administered to a subject diagnosed with a proteinuric kidney disease over a projected treatment period to an end point, wherein:

(a) urinary protein creatinine ratio (UPCR) of said subject is to be measured at a first time point prior to said treatment period and a second time point occurring prior to the end point but after the start of the treatment period and any reduction of said UPCR between said first and second time points is to be determined, and

(b) if the UPCR of said subject fails to show a reduction of at least a predetermined amount in the range of 15%-35% at said second time point, administration of voclosporin to the subject is to be discontinued and said administration is to be continued if said predetermined amount of reduction is shown.

15. The use of claim 14 wherein the concentration of -C3 or C4 in the blood of said subject is to be measured at said first and second time points and whether the concentration of C3 or C4 is normalized at said second time point is to be determined, and if said normalization of C3 or C4 is found, any discontinuing of or continuing administering voclosporin to the subject is to be reinstated, and if normalization has not occurred said discontinuing is to be maintained.

16. The use of claim 14 or 15 wherein an effective amount of mycophenolate mofetil (MMF) is to be administered to said subject.

17. The use of claim 14 or 15 wherein an effective amount of a corticosteroid is to be administered to said subject.

18. The use of claim 14 or 15 wherein said predetermined daily dosage is 39.5mg voclosporin BID or 31.6mg voclosporin BID or 23.7mg voclosporin BID or 15.8mg voclosporin BID or 7.9mg voclosporin BID.

19. Use of a composition comprising volclospoin in the manufacture of a medicament for treating a proteinuric kidney disease, wherein a predetermined daily dosage of voclosporin is to be administered to a subject diagnosed with lupus nephritis over a protocol

that consists of a projected treatment period of at least 8 weeks, wherein said the dosage of voclosporin is15.8/mg BID or 7.9/mg voclosporin BID and does not exceed 15.8 mg BID over the entire protocol and wherein said subject is to be administered voclosporin only in said protocol.