



US 20130345147A1

(19) **United States**

(12) **Patent Application Publication**
Feinerman et al.

(10) **Pub. No.: US 2013/0345147 A1**

(43) **Pub. Date: Dec. 26, 2013**

(54) **PREVENTION AND TREATMENT OF
OCULAR SIDE EFFECTS WITH A
CYCLOSPORIN**

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(21) Appl. No.: **13/957,772**

(22) Filed: **Aug. 2, 2013**

Related U.S. Application Data

(60) Continuation of application No. 12/825,116, filed on
Jun. 28, 2010, now Pat. No. 8,501,174, which is a

division of application No. 11/548,631, filed on Oct.
11, 2006, now Pat. No. 7,745,400.

(60) Provisional application No. 60/596,709, filed on Oct.
14, 2005, provisional application No. 60/597,431,
filed on Nov. 30, 2005, provisional application No.
60/805,509, filed on Jun. 22, 2006, provisional appli-
cation No. 60/805,577, filed on Jun. 22, 2006.

Publication Classification

(51) **Int. Cl.**
A61K 38/13 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 38/13** (2013.01)
USPC **514/20.5**

(57) **ABSTRACT**
Therapeutic methods are disclosed herein.

PREVENTION AND TREATMENT OF OCULAR SIDE EFFECTS WITH A CYCLOSPORIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This continuation application claims priority to: U.S. Provisional Patent Application No. 60/596,709, filed on Oct. 14, 2005; U.S. Provisional Patent Application No. 60/597,431, filed on Nov. 30, 2005; U.S. Provisional Patent Application, No. 60/805,577, filed on Jun. 22, 2006; U.S. patent application Ser. No. 11/548,631, filed Oct. 11, 2006, now U.S. Pat. No. 7,745,400; U.S. patent application Ser. No. 12/825,116, filed Jun. 28, 2010, now U.S. Pat. No. 8,501,174; and co-pending U.S. patent application Ser. No. 13/957,722, filed Aug. 2, 2013, all of which are expressly incorporated by reference herein.

DESCRIPTION OF THE INVENTION

[0002] Patients undergoing treatment with certain therapeutically active agents can have certain ocular conditions as a result of that treatment. In particular, patients undergoing chemotherapy with a therapeutically active agent effective for treatment of a cancer often have ocular conditions as a result of that treatment.

[0003] One embodiment is a method comprising administering a cyclosporin, an analog or derivative thereof, or a combination thereof, to an eye of a mammal in combination with administration of a therapeutically active agent to said mammal, said therapeutically active agent being a chemotherapy agent or an antiviral agent, wherein said method is effective in preventing or treating an ocular condition associated with the use of said therapeutically active agent.

[0004] "Administration of a therapeutically active agent to said mammal" means administration of the therapeutically active agent to the mammal in any way that a therapeutically active agent may be administered. Thus, administration of the therapeutically active agent is not limited to the eye, but may include systemic administration via oral, intravenous, rectal, or other means; or administration locally to any part of the body by injection, implantation, topical administration, or other means.

[0005] Administration of the therapeutically active agent need not exactly overlap in time with the administration of the cyclosporin, an analog or derivative thereof, or a combination thereof. For example, the cyclosporin, analog or derivative thereof, or a combination thereof might be administered to a mammal before the mammal receives any of the therapeutically active agent to avoid the onset of the ocular condition. In another example, the cyclosporin, analog or derivative thereof, or a combination thereof, might be administered after the mammal has begun to receive the therapeutically active agent. In another example, the cyclosporin, analog or derivative thereof, or a combination thereof, might be administered after the mammal has ceased receiving the therapeutically active agent. Administration of the cyclosporin, analog or derivative thereof, or a combination thereof might also be simultaneous with the administration of the therapeutically active agent. Thus, any time relationship may exist between the mammal receiving the therapeutically active agent and the cyclosporin, analog or derivative thereof, or a combination

thereof, provided that the use of the latter is reasonably related to treatment or prophylaxis of a condition associated with the former.

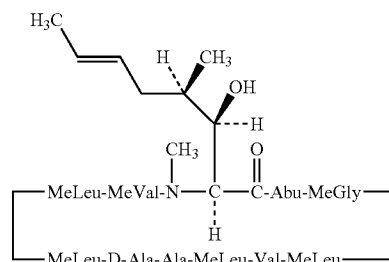
[0006] It may be convenient to provide a single pharmaceutical composition which comprises both (i) the cyclosporin, analog or derivative thereof, or a combination thereof and (ii) the therapeutically active agent when the agents are to be administered simultaneously.

[0007] It may be convenient to provide (i) the cyclosporin, analog or derivative thereof, or a combination thereof and (ii) the therapeutically active agent in form of a kit. For example, the agents may be packaged together. For example, (i) the cyclosporin, analog or derivative thereof, or a combination thereof and (ii) the therapeutically active agent may each be packaged in conventional pharmaceutical packaging such as boxes, jars, blister packs, vials, bottles, syringes etc., and the individually packaged components may then be combined to form a kit e.g. by the use of further packaging such as a box, or by joining up the individual packages. When in kit form, the agents can be taken independently of one another, thus allowing the user freedom to decide the temporal relationship between his use of each of the agents.

[0008] Use of a cyclosporin, or an analog or derivative thereof, including cyclosporin A, for the treatment of ocular conditions occurring in a person undergoing treatment with a therapeutically active agent for the treatment of cancer is contemplated. Accordingly, a particular patient group which may benefit from the present invention is that of persons having ocular conditions resulting from the use of a chemotherapy agent.

[0009] Also contemplated is use of a cyclosporin, or an analog or derivative thereof, including cyclosporin A, for the treatment of ocular conditions occurring in a person who is undergoing treatment with an antiviral agent. Accordingly, a particular patient group which may benefit from the present invention is that of persons having ocular conditions resulting from the use of an antiviral agent.

[0010] Also contemplated is use of a cyclosporin, or an analog or derivative thereof, including cyclosporin A, for the treatment of ocular conditions occurring in a person who is undergoing treatment with an immunomodulator. Accordingly, a particular patient group which may benefit from the present invention is that of persons having ocular conditions resulting from the use of an immunomodulator.



Cyclosporin A

[0011] Cyclosporin A is a cyclic peptide with immunosuppressive properties having the structure shown above. It is also known by other names including cyclosporine, cyclosporine A, ciclosporin, and ciclosporin A.

[0012] Other cyclosporins include cyclosporine b, cyclosporine D, cyclosporine G, which are well known in the art. Cyclosporin derivatives and analogs are also known in the art. For example, U.S. Pat. Nos. 6,254,860 and 6,350,442, incorporated by reference herein, illustrate several examples.

[0013] The ocular conditions to be prevented or treated are well known in the art. In particular, nasolacrimal stenosis, chemotherapy induced ocular toxicity, lacrimal duct stenosis, punctal stenosis, lacrimation, abnormal lacrimation (such as keratoconjunctivitis sicca), increased tearing, nasolacrimal blockage, keratitis, keratoconjunctivitis, conjunctivitis, or a combination thereof may be prevented or treated.

[0014] Also contemplated is a method comprising administering cyclosporin A topically to the eye of a person, wherein docetaxel is also administered to said person, wherein said method is effective in preventing or treating an ocular condition associated with the administration of docetaxel.

[0015] Although the ocular condition may be associated with any antiviral agent, the following

[0016] antiviral agents are contemplated in particular:

[0017] Zalcitabine, and

[0018] Rimantadine Hydrochloride.

[0019] Although the ocular condition may be associated with any chemotherapy agent, the following

[0020] chemotherapy agents are contemplated in particular:

[0021] Paclitaxel and derivatives thereof, such as Docetaxel

[0022] Doxorubicin Hydrochloride,

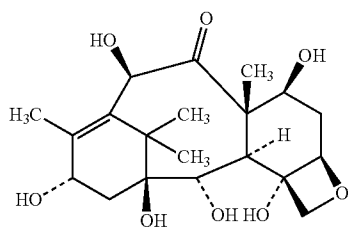
[0023] Irinotecan Hydrochloride,

[0024] Fluorouracil,

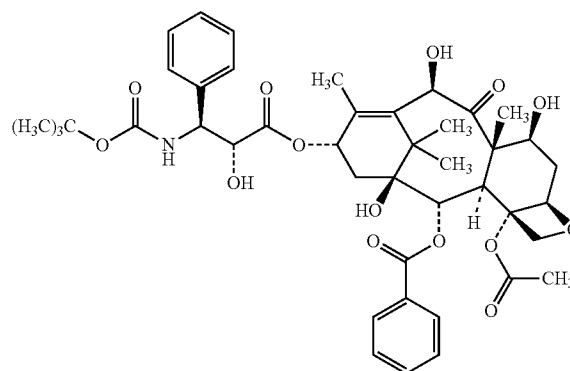
[0025] Imatinib Mesylate, and

[0026] Rituximab.

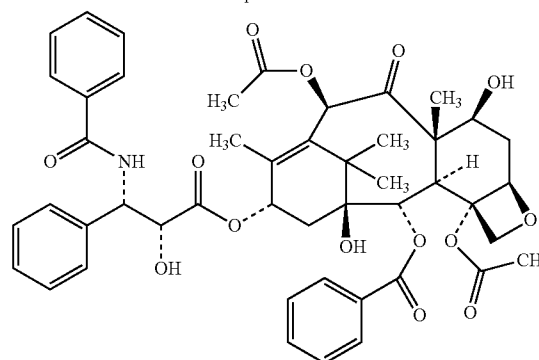
[0027] Derivatives of paclitaxel generally include the macrocycle shown below, where derivatives are formed at a hydroxyl moiety.



[0028] Chemotherapeutic compounds incorporating this structure are thus contemplated. For example, the structures of paclitaxel and docetaxel are shown below.



paclitaxel



Docetaxel

[0029] In one embodiment, the chemotherapy agent is docetaxel.

[0030] Although the ocular condition may be associated with any immunomodulator, the following

[0031] immunomodulators are contemplated in particular:

[0032] Interferon alfa-2b, Recombinant

[0033] Mycophenolate Mofetil, and

[0034] Mycophenolate Mofetil Hydrochloride.

[0035] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause lacrimal duct stenosis: docetaxel.

[0036] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause lacrimation:

[0037] interferon alfa-2b, recombinant,

[0038] doxorubicin hydrochloride,

[0039] irinotecan hydrochloride,

[0040] fluorouracil,

[0041] docetaxel, and

[0042] zalcitabine.

[0043] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause abnormal lacrimation:

[0044] mycophenolate mofetil,

[0045] mycophenolate mofetil hydrochloride,

[0046] imatinib mesylate,

[0047] rituximab, and

[0048] rimantadine hydrochloride.

[0049] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause keratitis:

[0050] Amantadine Hydrochloride,
 [0051] Erlotinib,
 [0052] Bexarotene, and
 [0053] Voriconazole.
 [0054] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause keratoconjunctivitis: Capecitabine.
 [0055] While not intending to limit the scope of the invention in any way, the following therapeutically active agents may cause conjunctivitis:
 [0056] Risedronate Sodium,
 [0057] Leflunomide,
 [0058] Mycophenolate Mofetil,
 [0059] Oxaliplatin,
 [0060] Cetuximab,
 [0061] Ribavirin,
 [0062] Rituximab,
 [0063] Basiliximab,
 [0064] Erlotinib,
 [0065] Capecitabine,
 [0066] Doxorubicin Hydrochloride,
 [0067] Imiquimod,
 [0068] Amphotericin B, liposomal,
 [0069] Zolpidem Tartrate,
 [0070] Glatiramer Acetate,
 [0071] Epirubicin Hydrochloride,
 [0072] Saquinavir,
 [0073] Enfuvirtide,
 [0074] Imatinib Mesylate,
 [0075] Gefitinib,
 [0076] Lamotrigine,
 [0077] Delavirdine Mesylate,
 [0078] Rituximab,
 [0079] Ivermectin,
 [0080] Palivizumab,
 [0081] Oseltamivir Phosphate,
 [0082] Bexarotene,
 [0083] Docetaxel,
 [0084] Abacavir Sulfate,
 [0085] Lamivudine,
 [0086] Zidovudine,
 [0087] Voriconazole,
 [0088] Nevirapine,
 [0089] Ribavirin, and
 [0090] Abacavir Sulfate.
 [0091] Additionally, one or more of the ocular conditions disclosed herein may be associated with the following therapeutically active agents: abacavir sulfate, amantadine hydrochloride, amphotericin B, basiliximab, bexarotene, capecitabine, cetuximab, delavirdine mesylate, docetaxel, doxorubicin hydrochloride, enfuvirtide, epirubicin hydrochloride, erlotinib, fluorouracil, gefitinib, glatiramer acetate, imatinib mesylate, imiquimod, interferon alfa-2b, irinotecan hydrochloride, ivermectin, lamivudine, lamotrigine, leflunomide, mycophenolate mofetil, mycophenolate mofetil hydrochloride, nevirapine, oseltamivir phosphate, oxaliplatin, palivizumab, ribavirin, rimantadine hydrochloride, risedr-

onate sodium, rituximab, saquinavir, voriconazole, zalcitabine, zidovudine, and zolpidem tartrate.

[0092] The therapeutically active agent is administered in the usual manner known in the art for the condition being treated.

[0093] Alternatively, a therapeutically active agent and cyclosporin A may be administered in a single composition.

[0094] Useful compositions are disclosed in the following patent applications, each of which is expressly incorporated by reference herein: U.S. patent application Ser. No. 11/181,409, filed on Jul. 13, 2005; U.S. patent application Ser. No. 11/181,509, filed on Jul. 13, 2005; U.S. patent application Ser. No. 11/181,187, filed on Jul. 13, 2005; U.S. patent application Ser. No. 11/181,178, filed on Jul. 13, 2005; U.S. patent application Ser. No. 11/181,428, filed on Jul. 13, 2005; U.S. patent application Ser. No. 11/255,821, filed on Oct. 19, 2005; U.S. patent application Ser. No. 11/161,218, filed on Jul. 27, 2005; and U.S. Provisional Patent Application Ser. No. 60/727,684, filed on Oct. 17, 2005.

[0095] In one embodiment, cyclosporin A is administered in the form of Restasis®, available from Allergan, Inc. The cyclosporin A is administered twice a day as indicated on the package insert.

[0096] Although there has been hereinabove described pharmaceutical compositions for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements, which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

1.-11. (canceled)

12. A method comprising administering an ophthalmically acceptable emulsion comprising cyclosporin A to a mammal before the mammal receives a therapeutically active agent, wherein the therapeutically active agent comprises paclitaxel, and wherein the method is effective in treating abnormal lacrimation.

13. The method of claim 12, wherein the ophthalmically acceptable emulsion comprises cyclosporin A at a concentration of about 0.05%.

14. The method of claim 13, wherein the ophthalmically acceptable emulsion further comprises castor oil, polysorbate 80, and high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

15. The method of claim 13, wherein the abnormal lacrimation is associated with keratoconjunctivitis.

16. The method of claim 13, wherein the abnormal lacrimation is the result of keratoconjunctivitis.

17. The method of claim 15, wherein the keratoconjunctivitis is associated with the therapeutically active agent.

18. The method of claim 16, wherein the keratoconjunctivitis is associated with the therapeutically active agent.

19.-24. (canceled)

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