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(54) Title: SYSTEMIC IMMUNOSUPPRESSION IN THE TREATMENT OF AGE RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

(57) Abstract: The invention provides a pharmaceutical composition comprising at least one anti-CD25 antibody composition and/or rapamycin or derivatives thereof, in a pharmaceutically and physiologically acceptable carrier, for use in an amount effective for use as a medicament for inhibiting the progression of choroidal neovascularization (CNV) and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of age-related macular degeneration (AMD) in a patient undergoing anti-VEGF treatment, and/or as a medicament for use in inhibiting the progression of diabetic retinopathy (DR), and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of DR in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.



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SYSTEMIC IMMUNOSUPPRESSION IN THE TREATMENT OF AGE RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/254,439, filed on October 23, 2009, the entire contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Age related macular degeneration (AMD) remains the leading cause of irreversible blindness in the United States and the Developed World. It has been calculated that, with the aging of the United States population, the prevalence of AMD will reach epidemic proportions, with an estimated 3 million United States citizens having the advanced form of the disease by 2020.

[0003] AMD is a single disorder which is often characterized as one of two types, non-exudative (dry form) or exudative (wet form). Although both types are bilateral and progressive, each type may reflect different pathological processes.

[0004] Both exudative (wet form) and non-exudative (dry form) of AMD are typically accompanied by the formation of drusen. Drusen are characterized by irregular, discrete, round yellow-white deposits which accumulate in the retina (in the back of the eye) between the basement membrane of the retinal pigment epithelium (RPE) and the rest of Bruch's membrane. The presence of drusen most likely reflect abnormalities in retinal pigment epithelial function. Drusen deposits can be further categorized into either hard drusen or soft drusen.

[0005] Exudative (wet form) AMD is characterized by serous or hemorrhagic separation of the retinal pigment epithelium or neurosensory layer. Patients may develop choroidal neovascularization (CNV), which is manifested as fluid accumulation, hemorrhage, and/or lipid exudation.

[0006] Another disease, diabetic retinopathy (DR) can also lead to blindness. The earliest stage of DR is characterized by retinal vascular abnormalities including microaneurysms (saccular out-pouchings from the capillary wall), intraretinal hemorrhages, and cotton-wool spots (nerve fiber layer infarctions). As DR progresses, the gradual closure of retinal vessels

results in retinal ischemia, giving rise to signs including venous abnormalities (beading, loops), intraretinal microvascular abnormalities, and increasing retinal hemorrhage and exudation. Non-proliferative diabetic retinopathy is graded as mild, moderate, severe, and very severe according to the presence and extent of the above lesions.

[0007] The more advanced stage of DR involves the formation of new blood vessels, induced by the retinal ischemia, which spread out either from the disc (neovascularization of the disc, NVD) or from elsewhere in the retina (neovascularization elsewhere, NVE). New blood vessels extending into the vitreous can cause vitreous hemorrhage and tractional retinal detachments associated with accompanying contractile fibrous tissue.

[0008] To date, the only treatment conclusively demonstrated to be of long term benefit for DR is focal laser photocoagulation.

[0009] The standard treatment for patients with AMD is injections of anti-VEGF compositions into the eye, and there have been studies that have shown that anti-VEGF therapy may be useful in DR. However, there are drawbacks associated with anti-VEGF treatment of AMD and DR, so that there still exists a desire for alternative treatment for patients with AMD and also DR.

BRIEF SUMMARY OF THE INVENTION

[0010] Advantageously, systemic treatment of patients having CNV associated with AMD, with anti-CD25 immunotherapy, slows the progression of CNV and/or AMD and reduces the number of VEGF treatment patients need.

[0011] Also, systemic treatment of patients having CNV associated with AMD with rapamycin, slows the progression of CNV and/or AMD and reduces the number of VEGF treatments patients need.

[0012] Accordingly, in an embodiment, the present invention provides a method for treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25 antibody composition, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0013] In another embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25

antibody composition in an amount effective to inhibit the progression of CNV associated with AMD.

[0014] In another embodiment, the present invention provides a method for treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0015] In an embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof in an amount effective to inhibit the progression of CNV associated with AMD.

[0016] In a further embodiment, the present invention provides a method of treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient a combination of at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0017] In yet another embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient the combination of at least one anti-CD25 antibody composition and rapamycin or a derivative thereof.

[0018] In accordance with another advantage, systemic treatment of patients having DR, with anti-CD25 immunotherapy, slows the progression of DR and reduces the number of VEGF treatment patients need.

[0019] It has also been found, in accordance with the present invention, that systemic treatment of patients having DR with rapamycin slows the progression of DR and reduces the number of VEGF treatments that patients need.

[0020] Accordingly, in an embodiment, the present invention provides a method for inhibiting the progression of DR in a patient undergoing anti-VEGF treatment, comprising periodically administering to the patient one anti-CD25 antibody composition in an amount effective to inhibit the progression of DR.

[0021] In yet a further embodiment, the present invention provides a method of treating a patient having DR and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25 antibody composition and rapamycin or a

derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0022] In another embodiment, the present invention provides a method for treating a patient having DR and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0023] Figure 1 is a schematic diagram showing the different treatment arms of a study.

[0024] Figure 2 shows the anti-VEGF injection history of each patient in the study.

[0025] Figure 3 shows the visual acuities and OCT measurements for both the study eyes and the fellow eyes of the patients.

[0026] Figure 4 shows the Grade 2 or 3 adverse events that occurred during the study.

DETAILED DESCRIPTION OF THE INVENTION

[0027] In an embodiment, the present invention provides a method for treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25 antibody composition, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0028] In another embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25 antibody composition.

[0029] In another embodiment, the present invention provides a method for treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0030] In an embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof, in an amount effective to inhibit the progression of CNV associated with AMD.

[0031] In a further embodiment, the present invention provides a method of treating a patient having CNV associated with AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient a combination of at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0032] In yet another embodiment, the present invention provides a method for inhibiting the progression of CNV associated with AMD in a patient having AMD and undergoing anti-VEGF treatment, comprising periodically administering to the patient the combination of at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, in an amount effective to inhibit the progression of CNV associated with AMD.

[0033] In another embodiment, the present invention provides a method for inhibiting the progression of DR in a patient undergoing anti-VEGF treatment, comprising periodically administering to the patient one anti-CD25 antibody composition in an amount effective to inhibit the progression of DR.

[0034] In yet a further embodiment, the present invention provides a method of treating a patient having DR and undergoing anti-VEGF treatment, comprising periodically administering to the patient at least one anti-CD25 antibody composition, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient. In an embodiment, the method of treating a patient having DR and undergoing anti-VEGF treatment, comprises periodically administering to the patient at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

[0035] In another embodiment, the present invention provides a method for treating a patient having DR and undergoing anti-VEGF treatment, comprising periodically administering to the patient rapamycin or a derivative thereof, in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient

[0036] Daclizumab (Zenapax®) is a humanized antibody directed against the alpha portion of the IL-2 (CD25) receptor that is found in activated T-cells. It is a recombinant monoclonal immunoglobulin of the human IgG1 isotype which is a composite of human (90%) and murine (10%) antibody sequences.

[0037] In an embodiment of the present invention, the anti-CD25 composition comprises daclizumab. It is contemplated that daclizumab can be administered to the patient through varying routes of administration. In one embodiment, the route of administration can be

systemic. Systemic routes of administration can include intravenous, parenteral, subcutaneous, intramuscular, intraarterial, intrathecal, and interperitoneal. In an alternate embodiment, daclizumab can be administered directly to the eye. This route of administration can include intraocular injection, periocular injection, or topical application, which could also include a device permitting slow release of the composition.

[0038] It will be understood that the anti-CD25 composition, daclizumab, is administered to a patient in a therapeutically effective amount sufficient to reduce the amount of anti-VEGF therapy given to the patient to treat AMD or DR symptoms. In an embodiment, the dosage amount of daclizumab for a patient is in a range from about 0.1 mg/kg to about 30 mg/kg. In another embodiment, the dosage amount of daclizumab for a patient is in a range from about 0.5 mg/kg to about 10 mg/kg. In yet another embodiment, the dosage amount of daclizumab for a patient is in a range from about 1 mg/kg to about 8 mg/kg.

[0039] In another embodiment, it is contemplated that daclizumab may be given in a loading dose. A loading dose is the first dose administered, and is a dose given in a greater amount than what would be administered in subsequent doses. For example, in an embodiment, a loading dose of daclizumab is administered in a range of about 5.0 mg/kg to about 15 mg/kg. In another embodiment, the loading dose of daclizumab is about 8 mg/kg.

[0040] In an embodiment of the present invention, daclizumab is administered to the patients periodically in accordance with a dosing regimen. It is contemplated that in an embodiment of the present invention, that the patients are administered daclizumab on, for example, a daily basis, every other day, three times a week, twice a week, weekly, biweekly, monthly or bimonthly schedule. In an embodiment of the present invention, the patients are administered daclizumab on a biweekly basis. In another embodiment of the present invention, the patients are administered daclizumab on a monthly basis. It is also contemplated that more than one dosing schedule may be used with the method of the present invention. For example, a patient may be administered daclizumab on a weekly or biweekly basis, and then have it administered on a monthly basis later on.

[0041] It is contemplated that other anti-CD25 antibodies can be used with the methods of the present invention. Examples of other anti-CD25 antibodies include RA8 (Arias, R.S., et al., Hybridoma, 26:119-30 (2007)), and basiliximab (Simulect® Novartis Rueil-Malmaison, France). In an embodiment of the present invention, basiliximab can be administered to the patient as the only anti-CD25 composition, or as an additional, anti-CD25 composition.

[0042] It is also contemplated that more than one anti-CD25 antibody can be administered to the patient in accordance with the present invention. In an embodiment the present invention provides a method of treating a patient having CNV associated with AMD or DR, and undergoing anti-VEGF treatment, comprising periodically administering to the patient the combination of two anti-CD25 antibody compositions, in amounts effective to reduce the amount of anti-VEGF treatments needed by the patient. For example, in an embodiment, the patient is administered a combination of daclizumab and basiliximab, each having a dose in a dose range for example, of about 0.1 mg/kg to about 30 mg/kg or from about 0.5 mg/kg to about 10 mg/kg, or in a range from about 1 mg/kg to about 8 mg/kg.

[0043] Rapamycin (Sirolimus®) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*, that inhibits T lymphocyte activation and proliferation in response to both antigenic and cytokine (IL-1 IL-2, IL-4, and IL-15) stimulation, by a mechanism that is distinct from that of other immuno-suppressants. Rapamycin also inhibits antibody production. In cells, rapamycin binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian target of sirolimus (mTOR), a key regulatory kinase.

[0044] Derivatives of rapamycin are known. For example, U.S. Patent No. 5,118,678 discloses carbamates of rapamycin that are useful as immunosuppressive, anti-inflammatory, antifungal, and antitumor agents. U.S. Patent No. 5,100,883 discloses fluorinated esters of rapamycin. U.S. Patent No. 5,118,677 discloses amide esters of rapamycin. U.S. Patent No. 5,130,307 discloses aminoesters of rapamycin. U.S. Patent No. 5,117,203 discloses sulfonates and sulfamates of rapamycin. U.S. Patent No. 5,194,447 discloses sulfonylcarbamates of rapamycin.

[0045] In an embodiment of the method of the present invention, the composition being administered to the patient suffering from AMD or DR, also comprises rapamycin and derivatives thereof. It is contemplated that rapamycin and its derivatives can be administered to the patient through varying routes of administration. In one embodiment, the route of administration can be systemic. Systemic routes of administration can include intravenous, parenteral, subcutaneous, intramuscular, intraarterial, intrathecal, and interperitoneal. In an alternate embodiment, rapamycin and its derivatives can be administered directly to the eye. This route of administration can include intraocular injection, periocular injection, or topical application, which could also include a device permitting slow release of the composition.

[0046] It will be understood that the rapamycin composition, is administered to a patient in a therapeutically effective amount sufficient to reduce the amount of anti-VEGF therapy given to the patient to treat AMD or DR symptoms. In an embodiment, the dosage amount of rapamycin and its derivatives for a patient is in a range from about 0.1 mg/kg to about 50 mg/kg. In another embodiment, the dosage amount of rapamycin and its derivatives for a patient is in a range from about 0.5 mg/kg to about 30 mg/kg. In yet another embodiment, the dosage amount of rapamycin and its derivatives, for a patient is in a range from about 1 mg/kg to about 5 mg/kg.

[0047] In another embodiment, it is contemplated that rapamycin or a derivative thereof is given in a loading dose. For example, in an embodiment, a loading dose of rapamycin is administered in a range of about 2.0 mg/kg to about 20 mg/kg, or in a range of about 8 mg/kg to about 16 mg/kg.

[0048] In an embodiment of the present invention, rapamycin or a derivative thereof is administered to the patients periodically in accordance with a dosing regimen. It is contemplated that in an embodiment of the present invention, that the patients are administered rapamycin on, for example, a daily basis, every other day, three times a week, twice a week, weekly, biweekly, monthly or bimonthly schedule. In an embodiment of the present invention, the patients are administered rapamycin every other day. It is also contemplated that more than one dosing schedule may be used in the method. For example, a patient is administered rapamycin on a daily or every other day basis, and then have it administered on a weekly basis later on.

[0049] It is also contemplated that a combination of at least one anti-CD25 antibody and rapamycin can be administered to the patient in accordance with the present invention. In an embodiment, the present invention provides a method of treating a patient having CNV associated with AMD or DR, and undergoing anti-VEGF treatment, comprising periodically administering to the patient, the combination of at least one anti-CD25 antibody and rapamycin or a derivative thereof, in amounts effective to reduce the amount of anti-VEGF treatments needed by the patient. For example, in an embodiment, the patient is administered a combination of daclizumab and rapamycin, wherein daclizumab has a dose in a dose range for example, of about 0.1 mg/kg to about 30 mg/kg or from about 0.5 mg/kg to about 10 mg/kg, or in a range from about 1 mg/kg to about 8 mg/kg, and the rapamycin has a dose in a dose range of about 0.1 mg/kg to about 50 mg/kg, or in a range of about 0.5 mg/kg to about 30 mg/kg, or in a range of about 1 mg/kg to about 5 mg/kg.

[0050] It is also contemplated that the present invention can be used as a medicament for a range of disease conditions. Therefore, in an embodiment, the present invention also provides a pharmaceutical composition comprising at least one anti-CD25 antibody composition, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, and most preferably for use as a medicament for inhibiting the progression of CNV and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of AMD in a patient undergoing anti-VEGF treatment.

[0051] With regard to the use of a medicament for inhibiting the progression of CNV and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of AMD in a patient undergoing anti-VEGF treatment, the at least one anti-CD25 antibody composition of the pharmaceutical composition includes daclizumab. In yet a further embodiment of the present invention, the pharmaceutical composition further comprises a second anti-CD25 antibody composition comprising basiliximab and physiologically acceptable carrier, in an amount effective for use in a medicament.

[0052] With regard to the use of a medicament for inhibiting the progression of CNV and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of AMD in a patient undergoing anti-VEGF treatment, the medicament provides a dose of at least one anti-CD25 antibody composition in range of about 0.1 mg/kg to about 30 mg/kg, preferably from about 0.5 mg/kg to about 10 mg/kg, and more preferably in a range from about 1 mg/kg to about 8 mg/kg.

[0053] In another embodiment the present invention also provides a pharmaceutical composition comprising at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, and most preferably for use as a medicament for inhibiting the progression of CNV and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of AMD in a patient undergoing anti-VEGF treatment. In a further embodiment, the medicament provides a dose of rapamycin or a derivative thereof in a range of 0.1 mg/kg to about 50 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, more preferably from about 2 mg/kg to about 20 mg/kg, and still more preferably from between about 1 mg/kg to about 5 mg/kg.

[0054] The medicament of the present invention can also be used to treat DR. Therefore, in an embodiment, the present invention also provides a pharmaceutical composition

comprising at least one anti-CD25 antibody composition, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, and most preferably for use as a medicament for inhibiting the progression of DR and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of DR in a patient undergoing anti-VEGF treatment.

[0055] With regard to the use of a medicament for inhibiting the progression of DR and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of DR in a patient undergoing anti-VEGF treatment, the at least one anti-CD25 antibody composition of the pharmaceutical composition includes daclizumab. In yet a further embodiment of the present invention, the pharmaceutical composition further comprises a second anti-CD25 antibody composition comprising basilixamab and physiologically acceptable carrier, in an amount effective for use in a medicament.

[0056] With regard to the use of a medicament for inhibiting the progression of DR and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of DR in a patient undergoing anti-VEGF treatment, the medicament provides a dose of at least one anti-CD25 antibody composition in range of about 0.1 mg/kg to about 30 mg/kg, preferably from about 0.5 mg/kg to about 10 mg/kg, and more preferably in a range from about 1 mg/kg to about 8 mg/kg.

[0057] In another embodiment the present invention also provides a pharmaceutical composition comprising at least one anti-CD25 antibody composition and rapamycin or a derivative thereof, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, and most preferably for use as a medicament for inhibiting the progression of DR and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of DR in a patient undergoing anti-VEGF treatment. In a further embodiment, the medicament provides a dose of rapamycin or a derivative thereof in a range of 0.1 mg/kg to about 50 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, more preferably from about 2 mg/kg to about 20 mg/kg, and still more preferably from between about 1 mg/kg to about 5 mg/kg.

[0058] In an embodiment, both the anti-CD25 composition and rapamycin or a derivative thereof can be combined with a carrier. Preferably, the carrier is a pharmaceutically acceptable carrier. With respect to pharmaceutical compositions, the carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the active compound(s), and by the route of

administration. The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, and diluents, are well-known to those skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active agent(s) and one which has no detrimental side effects or toxicity under the conditions of use.

[0059] The choice of carrier will be determined in part by the particular composition administered, as well as by the particular method used to administer the composition. Accordingly, there are a variety of suitable formulations of the pharmaceutical composition of the invention. The following formulations for parenteral, subcutaneous, intravenous, intramuscular, intraarterial, intrathecal and interperitoneal administration are exemplary and are in no way limiting. More than one route can be used to administer either the anti-CD25 composition or rapamycin or its derivatives, and in certain instances, a particular route can provide a more immediate and more effective response than another route.

[0060] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

[0061] Oils, which can be used in parenteral formulations, include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0062] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl- β -aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0063] Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic

surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5% to about 15% by weight. Suitable surfactants include polyethylene glycol sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

[0064] Injectable formulations are in accordance with the invention. The requirements for effective pharmaceutical carriers for injectable compositions are well-known to those of ordinary skill in the art (see, e.g., *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 15th ed., pages 622-630 (2009)).

[0065] For purposes of the invention, the amount or dose of the anti-CD25 antibody and/or rapamycin and its derivatives administered should be sufficient to effect, e.g., a therapeutic or prophylactic response, in the subject over a reasonable time frame. The dose will be determined by the efficacy of the particular composition and the condition of a human, as well as the body weight of a human to be treated.

[0066] The dose of the composition administered also will be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular composition. Typically, the attending physician will decide the dosage of the composition with which to treat each individual patient, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, the composition to be administered, route of administration, and the severity of the condition being treated.

[0067] It is contemplated that the patients to be treated using the methods of the present invention are suffering from AMD or DR. In particular, the AMD patients treated with the claimed method have drusen and are undergoing treatment with anti-VEGF compositions. The DR patients will often exhibit neovascularization similar to CNV. For purposes of the present invention, an anti-VEGF composition is a composition which inhibits vascular endothelial growth factors. Examples of such compositions include bevacizumab (trade

name Avastin®, Genentech/Roche), which is a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor (VEGF). They can also involve antibody derivatives such as ranibizumab (Lucentis®), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF, such as sunitinib (Sutent®), sorafenib (Nexavar®), axitinib, and pazopanib.

[0068] In an embodiment, the patients to be treated with the methods of the present invention are treated with an anti-VEGF composition prior to, and periodically after, administration of either an anti-CD25 composition, or rapamycin or a derivative thereof, or both. In an embodiment, the route of administration of the anti-VEGF composition is directly to the eye. In particular, the routes of administration can include intraocular injection, periocular injection, or topical application, which could also include a device permitting slow release of the composition.

[0069] In an embodiment, patients are treated with the anti-VEGF composition bevacizumab, intraocularly, at a dose range of about 0.1 mg/0.05 cc to about 5 mg/0.05 cc. In another embodiment, the dose range is about 1.0 mg/0.05 cc to about 3.0 mg/0.05 cc.

[0070] In another embodiment, patients are treated with the anti-VEGF composition ranibizumab, intraocularly, at a dose range of about 0.1 mg/0.05 cc to about 3 mg/0.05 cc; preferably about 0.5 mg/0.05 cc.

[0071] In an embodiment of the present invention, patients are treated periodically with the anti-VEGF composition in accordance with a dosing regimen. It is contemplated that in an embodiment of the present invention, that the patients are treated with the anti-VEGF composition on, for example, a biweekly, monthly, bimonthly or trimonthly schedule.

[0072] It will be understood that the effect of the methods of the present invention is to reduce the amount of anti-VEGF treatment that needs to be administered to a patient to treat, or prevent, or mitigate the progression of CNV and/or AMD, or DR in that patient. It was found that administration of anti-CD25 compositions and/or rapamycin and its derivatives, in accordance with the present invention, resulted in patients having significantly fewer treatments of anti-VEGF compounds to their affected eyes per month. For purposes of the present invention, a significant reduction in treatments of anti-VEGF compounds is defined as a relative reduction in treatment frequency of at least 10 percent or greater, when compared to untreated controls.

EXAMPLES

[0073] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[0074] A study was conducted at the Clinical Center, National Institutes of Health (NIH). The study protocol was reviewed and approved by the Institutional Review Board of the NIH and all procedures conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

[0075] The study was a pilot, phase I/II prospective, randomized, un-masked single-center trial that consisted of 3 systemic immunologic treatments and a control group with 6 months follow-up: daclizumab, rapamycin, infliximab and observation. Randomization was performed by the NIH pharmacy. All treatment arms (including observation) received standard care which included intraocular anti-VEGF or steroid injections at the treating physicians' discretion.

[0076] Participants who were 55 years or older with CNV associated with AMD were eligible. Eligibility further required that they have recurrent CNV requiring intravitreal injections of an anti-VEGF agent. The referring retinal physician made the decision as to which eye had active disease and required treatment and that eye therefore became the study eye.

[0077] Injections of either bevacizumab (Avastin® about 1.25 mg/0.05 cc or about 2.5 mg/0.1 cc) or ranibizumab (Lucentis® 0.5 mg) were given if there was recurrence of intraretinal or subretinal fluid as seen on ocular coherence tomography (OCT). Patients were required to have received intravitreal anti-angiogenic therapy within seven days of entry into this study. All patients demonstrated the presence of drusen larger than 63 μ m; vision in the study eye between 20/20 and 20/400; had either classic or occult CNV seen on fluorescein angiography; did not have an inflammatory or degenerative disease to explain the ocular findings; did not have a history of cancer in the past 5 years; and had no evidence of active tuberculosis or cardiac insufficiency.

[0078] During the study period, patients were seen at least monthly by their treating retinal consultant and received antiangiogenic therapy deemed necessary to treat their AMD regardless of the treatment arm they were assigned. Criterion for reinjection was detection of any intra or subretinal fluid on OCT. The number of injections in the study eye throughout the study was compared among the study arms. In addition the number of injections in the study eye during the study was also compared with "pre-study" injections in the same eye. Pre-study injection rates were calculated by total injection number divided by months over

which repeated injections were given for each participant. The in-study injection rate was calculated by injection number divided by the study duration (6 months). Only study eye injections were calculated (both for pre-study and in-study).

[0079] Patients were randomized (1:1:1:1) to one of the 3 systemic immunosuppressive agents (intravenous daclizumab, intravenous infliximab, or oral tablets of rapamycin) or observation (Figure 1).

[0080] Patients randomly assigned to daclizumab received about 8 mg/kg daclizumab intravenously at time zero, then about 4 mg/kg at week two and then about 2 mg/kg (i.v.) monthly for the rest of the 6 month study.

[0081] Patients randomly assigned to infliximab received about 3 mg/kg infliximab IV monthly for 6 months.

[0082] Patients randomly assigned to rapamycin received about 2 mg rapamycin in capsule form every other day for 6 months.

[0083] The Stratus™ OCT (software version 5.0), a time domain OCT instrument, was used (Carl Zeiss Meditec, Dublin, CA). Information on scanning modes and image analyses were obtained from the manufacturer. Scanning with the Stratus™ OCT was performed using the fast macular thickness map (FastMac) protocol, which acquires six evenly distributed 6 mm radial lines, consisting of 128 A-scans per line, intersecting at the fovea (total of 768 sampled points) within a scan time of 1.9 seconds. Scanning with the Cirrus™ HD-OCT was performed using the 512 X 128 scan pattern (Macular Cube protocol) where a 6 x 6 mm area on the retina was scanned with 128 horizontal lines, each consisting of 512 A-scans per line (total of 65,536 sampled points) within a scan time of 2.4 seconds.

[0084] Whole blood samples from patients were collected immediately before starting the protocol and at different time points after the beginning of the study. Staining for CD3 and CD56 (for NK cells) was performed in peripheral whole blood from patients. The surface markers were evaluated using a 4-color whole blood lysing-washing protocol (Leveziel, N., et al., Mol. Vis., 13:2153-9 (2007)) and analyzed by a FACSCaliber flow cytometer (BD Biosciences). All antibodies were obtained from BD Pharmingen. The data obtained from flow cytometry were analyzed using FlowJo software (Tree Star Inc., Ashland, OR). NK cells were noted in a previous publication (Li, Z., et al., J. Immunol., 174:5187-91 (2005)) to be elevated in uveitis patients receiving daclizumab and thus NK cells were gated on CD56, CD3 staining. CD56 bright cells were gated on either CD56bright CX3CR1 negative/CD3

negative or CD56bright CXCR3positive CD3 negative. The results are represented as the percentage of CD56bright subset in the CD56-positive CD3-negative NK subpopulation.

[0085] A 4-color whole blood flow cytometry staining protocol was used to analyze surface expression levels of CD3, CD4 or CD8 on T cells, CD22 on B cells and CD56 on NK cells, as well as CD11b and CD11c on monocytes. Surface expression of chemokine/chemokine receptors (CX3CR1, CXCR3, CCR4, CCR5 and CCR7) and IL-2R α (CD25) and IL-2R β (CD122) were also examined. Data were analyzed using the FlowJo software (Tree Star). The lymphocytes and monocytes were gated based on forward scatter plot (FSC) vs. side scatter plot (SSC).

[0086] The expression levels of chemokine/chemokine receptors and IL-2 receptor subunits on T, B, NK cells and monocytes and subsets of T and NK cells, were analyzed based on gating on positive staining for anti-CD3, anti-CD8, and anti-CD56. The percentages of the positive cells from all patients at different time points during the course of the treatment were compared for changes of expression levels. Statistical analysis was by a Student's t test.

[0087] A total of 13 patients met the criteria for the study and were enrolled from Sept 2006 to May 2008. There were 12 women and one man. The mean age of the participants was 80 years (60-92 years). The mean time to begin anti-VEGF injections before entering the study was similar in all groups: 16 months for daclizumab, 14 months for rapamycin, 13 months for infliximab, and 16 months for the observation group. Twelve of the 13 enrolled patients completed the six month follow-up. One patient withdrew from the study prior to 6 months (patient # 7 completed 3.5 months). This patient withdrew for non-study reasons; the patient fell during the follow up period resulting in several fractures and the inability to continue the study follow up.

[0088] Figure 2 shows the anti-VEGF injection history for each patient. Patients are grouped by the study arm to which they were assigned. The pre-study and in-study injection rates are provided for each patient with the mean and median for each group. The lesion types varied between groups, but occult lesions slightly predominated (Fig. 2). All patients in the daclizumab group were classified as having occult CNV, in the rapamycin group 1/3 were classified as occult and 2/3 as classic, and in the infliximab group, there were a mixed group of membranes. Monthly rates of anti-VEGF injections were about 0.42 and about 0.34 for daclizumab and rapamycin respectively, compared with about 0.83 for both the control group and the infliximab group during the 6 month study period. Injection rates during the study

compared with pre-study rates showed a decrease in the patients treated with rapamycin and daclizumab from a median of 0.67 injections per month (pre-study) to a median of 0.34 and from about 0.73 to about 0.42, respectively; no decrease was seen for either infliximab or observation (Fig. 2).

[0089] Figure 3 shows the visual acuities and OCT measurements for both the study eyes and the fellow eyes. Study eyes in all groups maintained approximately stable visual acuities over the 6 month follow-up period; OCTs performed in all the treatment groups at the end of the study were also similar to those obtained at baseline.

[0090] Figure 4 shows the Grade 2 or 3 adverse events that occurred during the study. None of the adverse events required cessation of the study medication. Rapamycin has been reported to be associated with an increase in serum cholesterol levels. However, no clinically important changes in serum cholesterol levels between baseline and six months were seen and no patient required any change in cholesterol lowering medication during the study period.

[0091] Study patients were monitored for possible immune alterations in their peripheral blood. When compared with age matched controls, no differences in T cell and monocyte subgroups were noted in any of the therapeutic arms. However, in three patients receiving daclizumab, an increase in the CD56 bright NK cells was noted in the 2 tested at 8 months after the initiation of daclizumab therapy (data not shown). This subgroup increase has been seen in uveitis patients receiving this medication.

[0092] It was found that over the 6 month period of the study two medications, daclizumab and rapamycin, appeared to significantly decrease the patients' need for anti-VEGF intravitreal injections by approximately half, compared with observation or the infliximab group.

[0093] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0094] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not

limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0095] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A pharmaceutical composition comprising at least one anti-CD25 antibody composition, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, preferably for use as a medicament for inhibiting the progression of choroidal neovascularization (CNV) and/or for reducing the amount of anti-VEGF treatments needed by the patient associated with the treatment of age-related macular degeneration (AMD) in a patient undergoing anti-VEGF treatment.

2. The pharmaceutical composition of claim 1, wherein the at least one anti-CD25 antibody composition includes daclizumab.

3. The pharmaceutical composition of either of claims 1 or 2, further comprising a second anti-CD25 antibody composition comprising basilixamab and a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament.

4. The pharmaceutical composition of any of claims 1-3, wherein the medicament provides a dose of at least one anti-CD25 antibody composition in range of about 0.1 mg/kg to about 30 mg/kg, preferably from about 0.5 mg/kg to about 10 mg/kg, and more preferably in a range from about 1 mg/kg to about 8 mg/kg.

5. The pharmaceutical composition of any of claims 1-4, further comprising rapamycin or a derivative thereof in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

6. The pharmaceutical composition of claim 5, wherein the medicament provides a dose of rapamycin or a derivative thereof in a range of 0.1 mg/kg to about 50 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, more preferably from about 2 mg/kg to about 20 mg/kg, and still more preferably from between about 1 mg/kg to about 5 mg/kg.

7. A pharmaceutical composition comprising at least one anti-CD25 antibody composition, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, preferably for use as a

medicament for inhibiting the progression of diabetic retinopathy (DR) in a patient undergoing anti-VEGF treatment.

8. The pharmaceutical composition of claim 7, wherein the at least one anti-CD25 antibody composition includes daclizumab.

9. The pharmaceutical composition of either of claims 7 or 8, further comprising a second anti-CD25 antibody composition comprising basilixamab and a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament.

10. The pharmaceutical composition of any of claims 7-9, wherein the medicament provides a dose of at least one anti-CD25 antibody composition in range of about 0.1 mg/kg to about 30 mg/kg, preferably from about 0.5 mg/kg to about 10 mg/kg, and more preferably in a range from about 1 mg/kg to about 8 mg/kg.

11. The pharmaceutical composition of any of claims 7-10, further comprising rapamycin or a derivative thereof in an amount effective to reduce the amount of anti-VEGF treatments needed by the patient.

12. The pharmaceutical composition of claim 11, wherein the medicament provides a dose of rapamycin or a derivative thereof in a range of 0.1 mg/kg to about 50 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, more preferably from about 2 mg/kg to about 20 mg/kg, and still more preferably from between about 1 mg/kg to about 5 mg/kg.

Figure 1

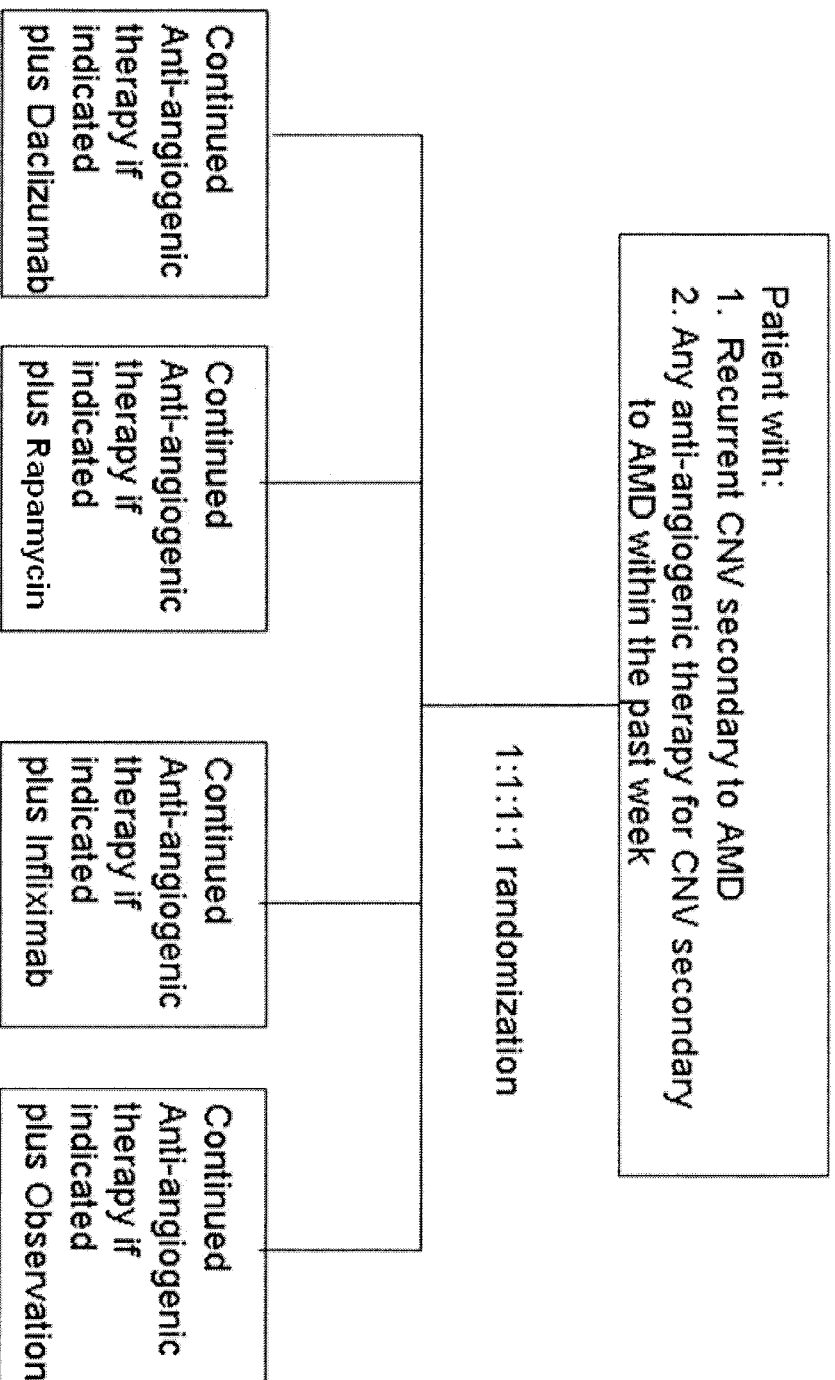


Figure 2

Anti-VEGF injection history per patient during the study

patient	Tx arm	Study eye	pre-study	in-study	pre-study		in-study		Lesion type
					median/ mean	Median/ mean			
3	dacliczumab	os	0.6	0.34	0.725	0.42			occult
9	dacliczumab	od	0.74	0.34	0.805	0.5025			occult
13	dacliczumab	os	1.17	0.83					occult
8	dacliczumb	od	0.71	0.5					occult
2	infliximab	od	0.67	0.5	0.7	0.83			min classic
6	infliximab	os	0.93	0.83	0.7666667	0.776667			occult
10	infliximab	os	0.7	1					classic
4	observation	os	0.5	0.83	0.67	0.83			occult
5	observation	od	0.75	0.5	0.64	0.776667			min classic
11	observation	od	0.67	1					classic
1	sirolimus	os	1	0.5	0.67	0.34			occult
7	sirolimus	od	0.44	0.29	0.70333333	0.376667			classic
12	sirolimus	od	0.67	0.34					classic

FIGURE 3

Table 3 Visual Acutities and OCT measurements for the Study Eyes

Patient #	Baseline		6th month		Baseline		6th month		Baseline		6th month	
	Vision Study Eye	Vision Study Eye	Vision Study Eye	Vision Study Eye	Other Vision Eye	Other Vision Eye	OCT Study Eye	OCT Study Eye	OCT Other Eye	OCT Other Eye	OCT Study Eye	OCT Other Eye
Sirolimus												
1	20/40	20/25	20/400	20/640	20/640	20/640	234	230	211	203		
7	20/63	20/50	20/640	20/640	20/640	20/640	361	239	242	186		
12	20/32	20/32	20/32	20/32	20/32	20/32	327	264	226	205		
Daclizumab												
3	20/40	20/40	20/40	20/32	20/32	20/32	216	189	352	206		
8	20/32	20/32	20/32	20/32	20/32	20/32	185	208	218	149		
9	20/250	20/250	20/63	20/40	20/40	20/40	297	196	215	210		
13	20/50	20/40	20/25	20/20	20/20	20/20	329	344	305	317		
Infliximab												
2	20/40	20/32	20/63	20/125	20/125	20/125	205	177	190	181		
6	20/250	20/800	20/63	20/80	20/80	20/80	290	243	262	252		
10	20/50	20/32	20/125	20/125	20/125	20/125	291	288	453	347		
Observation												
4	20/63	20/63	20/40	20/25	20/25	20/25	229	196	189	171		
5	20/50	20/25	CF	CF	CF	CF	426	225	270	213		
11	20/32	20/50	20/200	20/63	20/63	20/63	318	305	158	169		

FIGURE 4

TABLE 4 List of Grade 2 or 3 Adverse Events that Occurred During the Study

Participant Number	Category	Description	Intervention Required	Inpatient Care	Outcome	Effect on Therapy	Related to Agent	Severity
3	Neurology	Episode of right sided numbness	Other	No	Recovered, no residual effects	Held	Possibly	Severe/Grade 3
7	Cardiovascular	Irregular heart rate	Other	Yes	Recovered, with sequelae	Discontinued	Possibly	Severe/Grade 3
	Metabolic	electrolyte imbalance	Other	Yes	Recovered, no residual effects	Discontinued	Possibly	Severe/Grade 3
	Trauma	fall	Other	Yes	Recovered, with sequelae	Discontinued	Possibly	Severe/Grade 3
8	Neurology	sciatica to left leg and hip/back	Monitoring	No	Persistent condition not expected to resolve	None	Not related	Moderate/Grade 2
	GI	S/P colonoscopy diagnosed with colitis	Rx med	No	Persistent condition	Held	Remotely	Moderate/Grade 2
10	Dermatology	Rash arms bilateral	Rx med	No	Recovered, no residual effects	None	Not related	Moderate/Grade 2
12	Pulmonary	Bronchitis	Rx med	No	Recovered, no residual effects	None	Possibly	Moderate/Grade 2
	Other	elevated lipids	Rx med	No	Recovered, no residual effects	None	Probably	Moderate/Grade 2
	Musculoskeletal	Pain in back between shoulder blades	Rx med	No	Recovered, no residual effects	Held	Possibly	Moderate/Grade 2
	Musculoskeletal	Poly/malgia Rheumatica	Rx med	No	Recovered, no residual effects	None	Not related	Moderate/Grade 2
	Pulmonary	Dry persistent cough	Rx med	No	Recovered, no residual effects	None	Not related	Moderate/Grade 2