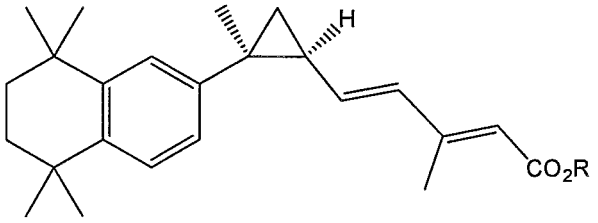
[0008a] In one aspect there is provided a use of a RXR agonist in the manufacture of a medicament for the treatment of an autoimmune disease, wherein a therapeutically effective amount of the medicament is to be administered in combination with a thyroid hormone to an individual in need thereof; wherein the RXR agonist has the structure of Formula II

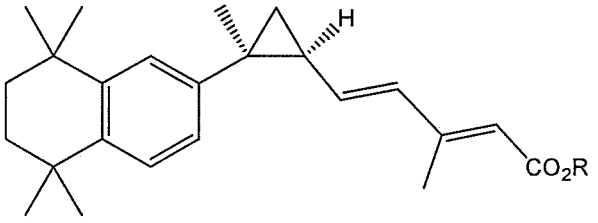


(II);

wherein R is H or lower alkyl of 1 to 6 carbons, bexarotene, or LG268 or a pharmaceutically acceptable salt thereof; and

wherein the combination to be administered shows greater efficacy in the treatment of the autoimmune disease than either the medicament or the thyroid hormone alone.

[0009] In certain embodiments, the RXR agonist is a selective RXR agonist having the structure of Formula II



(II),

wherein R is H or lower alkyl of 1 to 6 carbons.

[0010] In some embodiments, the RXR agonist is a selective RXR agonist comprising 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid. In other embodiments, the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid ethyl ester. In yet other embodiments, the RXR agonist is bexarotene. And, in still other embodiments, the RXR agonist is LG268. In some embodiments, the thyroid hormone is thyroxine.

[0011] In some embodiments, the therapeutically effective amount of the RXR agonist is about 0.001 mg/day to about 1000 mg/day. In other embodiments, the therapeutically effective amount of the ester of a RXR agonist is about 0.001 mg/day to about 1000 mg/day. In yet other embodiments, the therapeutically effective amount of the RXR agonist is about 10 mg/day to about 1000 mg/day, about 1.0 mg/day to about 100 mg/day, or about 1 mg/day to about 20 mg.day. In some embodiments, the dose of thyroxine is about 12.5 µg/day to about 250 µg/day.

[0012] In some embodiments, the RXR agonist is administered by nasal administration. In other embodiments, the RXR agonist and thyroxine are both administered by nasal administration. In other embodiments, the RXR agonist is administered orally. In yet other embodiments, the thyroxine is administered orally. In some embodiments, the thyroxine is administered subcutaneously.

[0013] In certain embodiments, the RXR agonist and the thyroxine are both administered substantially simultaneously. In other embodiments, the RXR agonist and thyroxine are administered on different schedules.

[0014] In certain embodiments, the method treats an autoimmune disease selected from the group consisting of acute disseminated encephalomyelitis (ADEM), Addison's disease, an allergy, allergic rhinitis, anti-phospholipid antibody syndrome (APS), an arthritis, asthma, acquired immunodeficiency syndrome (AIDS), autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, bullous pemphigoid, celiac disease, Chagas

heptadienoic acid, and thyroxine; and wherein administration of the combination reduces the severity of the autoimmune disease in the individual and more effectively than either the RXR agonist or thyroxine alone.

[0023a] In yet another aspect, there is provided the use of 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid (IRX4204) in the manufacture of a medicament for the treatment of an autoimmune disease, comprising a therapeutically effective amount of the medicament to be administered in combination with a therapeutically acceptable amount of thyroxine to an individual in need thereof; wherein the combined administration reduces the severity of the autoimmune disease in the individual more effectively than either the IRX4204 or thyroxine alone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. 1 shows RXR agonist activation of transcription from RXRα, RXRβ, RXRγ, RARα, RARβ, and RARγ using transactivation assays.

[0025] FIG. 2 shows that RXR agonists combined with thyroid hormone attenuate experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice.

[0026] FIGS. 3A-B shows that RXR agonists reduce leukocyte infiltration into the central nervous system. FIG. 3A depicts the number of $CD4^+$ cells and FIG. 3B depicts the number of $CD11c^+$ $CD11b^+$ cells (myeloid DC) in mice treated with the selective RXR agonist IRX4204 (4204) versus the vehicle control.

[0027] FIG. 4 shows RXR agonists attenuate EAE in SJL mice.

[0028] FIGS. 5A-D shows that IRX4204 selectively activates RXR-Nurr1 heterodimers. Transactivation assay of IRX4204 (194204, Formula III) for farnesoid X receptor FXR (FIG. 5A); for liver X receptors LXRα and LXRβ (FIG. 5B); for peroxisome proliferator-activated receptor PPARγ (FIG. 5C); and for Nurr1 receptor in the presence or absence of RXR (FIG. 5D).

[0029] FIG. 6 shows the percentage of green fluorescent protein (EGFP) positive oligodendrocytes after culture of oligodendrocyte precursor cells derived from embryonic mouse brains with IRX4204 and thyroid hormone.

[0030] FIG. 7 depicts effects of selective RXR agonist IRX4204 on EAE in mice,

[0031] FIGS. 8A-B depicts expression of CCR6 (FIG. 8A) and CD49d (FIG. 8B) on splenocytes from EAE mice treated with 200 μg/day of IRX4204 or control

[0032] FIGS. 9A-D depicts quantification (FIG. 9A) and frequency (FIG. 9B) of CD4+CD25hi cells, total number of effector and memory CD4 T cells (FIG. 9C), and total

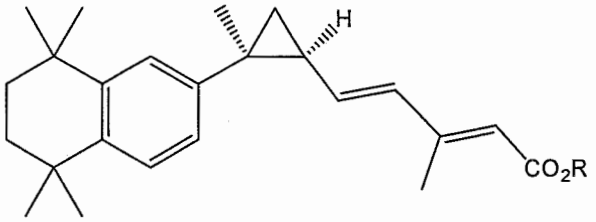
number of activated CD4 T cells (FIG. 9D) in splenocytes from EAE mice treated with 200 µg/day of IRX4204 or control.

[0033] FIG. 10 depicts the total number of infiltrating CD4 T cells in the CNS of EAE mice treated with 200 µg/day of IRX4204 or control.

[0034] FIGS. 11A-D depicts re-stimulation of the infiltrating lymphocytes of FIG. 10 to determine expression of interferon gamma (IFNγ) (FIG. 11A), IL-17A (FIG. 11B), tumor necrosis factor (TNF) (FIG. 11C), and IL-4 (FIG. 11D).

CLAIMS

1. Use of a RXR agonist in the manufacture of a medicament for the treatment of an autoimmune disease, wherein a therapeutically effective amount of the medicament is to be administered in combination with a thyroid hormone to an individual in need thereof; wherein the RXR agonist has the structure of Formula II



(II);

wherein R is H or lower alkyl of 1 to 6 carbons, bexarotene, or LG268 or a pharmaceutically acceptable salt thereof; and

wherein the combination to be administered shows greater efficacy in the treatment of the autoimmune disease than either the medicament or the thyroid hormone alone.

2. The use according to Claim 1, wherein is the RXR agonist is a selective RXR agonist comprising 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid.

3. The use according to Claim 1, wherein the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic ethyl ester .

4. The use according to Claim 1, wherein the RXR agonist is bexarotene.

5. The use according to Claim 1, wherein the RXR agonist is LG268.

6. The use according to Claim 1, wherein the thyroid hormone is thyroxine.

7. The use according to Claim 1, wherein the therapeutically effective amount of an ester of the RXR agonist having the structure of Formula II is about 0.001 mg/day to about 1000 mg/day.

8. The use according to Claim 1, wherein the therapeutically effective amount of the RXR agonist is about 0.001 mg/day to about 1000 mg/day.

9. The use according to Claim 1, wherein the therapeutically effective amount of the RXR agonist is about 1 mg/day to about 100 mg/day.

10. The use according to Claim 6, wherein the therapeutically effective amount of thyroxine is about 12.5 µg/day to about 250 µg/day.

11. The use according to Claim 1, wherein the RXR agonist is to be administered by nasal administration.

12. The use according to Claim 6, wherein the RXR agonist and thyroxine are both to be administered by nasal administration.

13. The use according to Claim 1, wherein the RXR agonist is to be administered orally.

14. The use according to Claim 6, wherein the RXR agonist and the thyroxine are both to be administered substantially simultaneously.

15. The use according to Claim 6, wherein the RXR agonist and thyroxine are to be administered on different schedules.

16. The use according to Claim 6, wherein the thyroxine is to be administered orally.

17. The use according to Claim 6, wherein the thyroxine is to be administered subcutaneously.

18. The use according to Claim 1, wherein the disease is selected from the group consisting of cute disseminated encephalomyelitis (ADEM), Addison's disease, an allergy, allergic rhinitis, anti-phospholipid antibody syndrome (APS), an arthritis, asthma, acquired immunodeficiency syndrome (AIDS), autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, bullous pemphigoid, celiac disease, Chagas disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus type 1 (IDDM), endometriosis, a gastrointestinal disorder, a glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis, hidradenitis suppurativa, idiopathic thrombocytopenic purpura, interstitial nephritis, interstitial cystitis, a lupus, morphea, multiple sclerosis (MS), myasthenia gravis, a myopathy, myositis, narcolepsy, neuromyotonia, pemphigus vulgaris, pernicious anaemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, a pulmonary fibrosis, recurrent disseminated encephalomyelitis, rheumatic fever, schizophrenia, scleroderma, Sjögren's syndrome, a skin disorder, tenosynovitis, uveitis, a vasculitis, and vitiligo.

19. The use according to Claim 18, wherein the arthritis is monoarthritis, oligoarthritis, polyarthritis, osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, septic arthritis, spondyloarthropathy, gout, pseudogout, or Still's disease.

20. The use according to Claim 18, wherein the gastrointestinal disorder is an irritable bowel disease or an inflammatory bowel disease.

21. The use according to Claim 20, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

22 The use according to Claim 18, wherein the lupus is discoid lupus erythematosus, drug-induced lupus erythematosus. lupus nephritis, neonatal lupus, subacute cutaneous lupus erythematosus, or systemic lupus erythematosus.

23. The use according to Claim 18, wherein the myopathy is dermatomyositis, inclusion body myositis, or polymyositis.

24. The use according to Claim 18, wherein the skin disorder is dermatitis, eczema, statis dermatitis, hidradenitis suppurativa, psoriasis, rosacea, or scleroderma.

25. The use according to Claim 18, wherein the vasculitis is Buerger's disease, cerebral vasculitis, Churg-Strauss arteritis, cryoglobulinemia, essential cryoglobulinemic vasculitis, giant cell arteritis, Golfer's vasculitis, Henoch-Schonlein purpura, hypersensitivity vasculitis, Kawasaki disease, microscopic polyarteritis/polyangiitis, polyarteritis nodosa, polymyalgia rheumatica (PMR), rheumatoid vasculitis, Takayasu arteritis, or Wegener's granulomatosis.

26. The use according to Claim 1, wherein the autoimmune disease is psoriasis, rheumatoid arthritis, glomerulonephritis, pulmonary fibrosis, or an inflammatory bowel disease.

27. Use of 3,7-dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]2(E),4(E) heptadienoic acid (IRX4204) in the manufacture of a medicament for the treatment of an autoimmune disease, wherein a therapeutically effective amount of the medicament is to be administered in combination with a therapeutically acceptable amount of thyroxine to an individual in need thereof; wherein the combined administration reduces the severity of the autoimmune disease in the individual more effectively than either the IRX4204 or thyroxine alone.