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(54) Titre : METHODES, AGENTS ET COMPOSITIONS POUR LE TRAITEMENT D'ETATS INFLAMMATOIRES
(54) Title: METHODS, AGENTS AND COMPOSITIONS FOR TREATMENT OF INFLAMMATORY CONDITIONS

(57) Abrégé/Abstract:
The present invention relates to the screening, diagnosis, prognostic evaluation, and treatment or prevention of age associated inflammation, chronic inflammation, and inflammatory diseases. In particular, the present invention relates to treating or preventing inflammatory diseases (e.g. rheumatoid arthritis or spondyloarthritis) or patients with inflammatory peripheral GnRH with GnRH antagonists or drugs that lower the effects of GnRH.

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(54) **Title**: METHODS, AGENTS AND COMPOSITIONS FOR TREATMENT OF INFLAMMATORY CONDITIONS

(57) **Abstract**: The present invention relates to the screening, diagnosis, prognostic evaluation, and treatment or prevention of age associated inflammation, chronic inflammation, and inflammatory diseases. In particular, the present invention relates to treating or preventing inflammatory diseases (e.g. rheumatoid arthritis or spondyloarthritis) or patients with inflammatory peripheral GnRH with GnRH antagonists or drugs that lower the effects of GnRH.

Claims

1. A GnRH antagonist for use in the treatment or prevention of an inflammatory condition in a subject, selected from an inflammatory disease, chronic inflammation, age-related inflammation or inflammatory peripheral GnRH, wherein said GnRH antagonist is for long-term administration to said subject for a period of at least 12 weeks.

2. The GnRH antagonist for use according to claim 1, wherein said inflammatory disease is rheumatoid arthritis, an inflammatory bowel disease, a spondyloarthritis, systemic sclerosis (scleroderma), psoriasis, nephritis, multiple sclerosis or osteoarthritis.

3. The GnRH antagonist for use according to claim 1 or claim 2, wherein said disease is rheumatoid arthritis.

4. The GnRH antagonist for use according to claim 1 or claim 2, wherein said inflammatory disease is ankylosing spondylitis.

5. The GnRH antagonist for use according to claim 2 wherein said inflammatory bowel disease is colitis or Crohn's disease.

6. The GnRH antagonist for use according to claim 1, wherein said GnRH antagonist is for use in treating or preventing osteoporosis or for increasing bone mineral density.

7. The GnRH antagonist for use according to claim 1, wherein said antagonist is for use in treating a cardiovascular disease or metabolic syndrome, or for decreasing the risk of a cardiovascular event or of developing coronary heart disease or metabolic syndrome by treating one or more risk factors for cardiovascular disease in a subject.

8. The GnRH antagonist for use according to claim 7, wherein said GnRH antagonist decreases HBA1c, decreases blood pressure, or increases HDL levels in said subject.

9. The GnRH antagonist for use according to claim 7, wherein said GnRH antagonist is for use in decreasing blood pressure.

10. The GnRH antagonist for use according to claim 1, wherein the inflammatory condition is systemic chronic inflammation.

11. The GnRH antagonist for use according to claim 1 or claim 10, wherein the inflammatory condition is age-related systemic chronic inflammation.

12. The GnRH antagonist for use according to claim 10 or claim 11, wherein the systemic chronic inflammation is low-level inflammation.

13. The GnRH antagonist for use according to claim 1 or claim 10, wherein the inflammatory condition is cancer inflammation.

14. The GnRH antagonist for use according to any one of claims 1 or 10 to 12, to treat or prevent low level systemic chronic inflammation in a subject who is without overt clinical symptoms of inflammatory disease.

15. The GnRH antagonist for use according to any one of claims 1 or 10 to 12 to treat or prevent peripheral inflammatory GnRH in a subject who exhibits a level of peripheral GnRH which is 300 pg/ml or above.

16. The GnRH antagonist for use according to claim 15, wherein the subject is healthy or is without overt clinical symptoms of inflammatory disease,

17. The GnRH antagonist for use according to any one of claims 1 to 16, wherein the GnRH antagonist is in the form of a conjugate with a polymer which serves to inhibit passage of the GnRH antagonist across the blood brain barrier.

18. The GnRH antagonist for use according to claim 17, wherein the polymer is a polypeptide, a polyethylene glycol (PEG) or a polysaccharide.

19. The GnRH antagonist for use according to any one of claims 1 to 18, wherein said GnRH antagonist is used in combination with one or more additional active agents.

20. The GnRH antagonist for use according to claim 19, wherein the additional active agent is an agent useful for the treatment of inflammation, particularly an agent useful in the

treatment of an inflammatory disease, including an inflammatory disease as defined in any one of claims 2 to 9.

21. The GnRH antagonist for use according to claim 19 or claim 20, wherein the GnRH antagonist and additional active agent have a synergistic effect.

22. The GnRH antagonist for use according to any one of claims 19 to 21, wherein the GnRH is used in combination with an additional active agent which is a sex hormone, including oestrogen or testosterone, or an agent useful in sex hormone substitution therapy, including LH or FSH.

23. The GnRH antagonist for use according to claim 22, wherein the sex hormone is titrated to a desired or selected level.

24. The GnRH antagonist for use according to any one of claims 19 to 23, wherein the additional active agent is selected from an anti-rheumatic agent, an non-steroidal anti-inflammatory drug (NSAID), a biologic agent, an analgesic, a biologic agent, a steroid, a glucocorticoid, an agent used to treat osteoporosis and an agent used to treat multiple sclerosis.

25. The GnRH antagonist for use according to any one of claims 19 to 24, wherein said additional active agents are selected from the group consisting of methotrexate, famprydine, daivobet, oestrogen and testosterone.

26. The GnRH antagonist for use according to any one of claims 1 to 25, wherein said GnRH antagonist is selected from the group consisting of cetrorelix, elagolix, ganirelix, abarelix, ASP1707, relugolix, degarelix, detirelix, iturelix, ozarelix, prazarelix, ramorelix, teverelix, a spiroindoline derivative, or a pyrrole, pyrazole, pyridinone, pyrimidinone, pyrrolidine, imidazole, imidazoline, quinolinone, quinoline, quinazonline, indole, furamide, oxazole, triazine-triole, pyrazinone, thiazole, or carbazole derivative, preferably wherein the GnRH antagonist is ASP1707.

27. The GnRH antagonist for use according to any one of claims 1 to 26, wherein said GnRH antagonist is for administration for at least five months.

28. The GnRH antagonist for use according to any one of claims 1 to 27, wherein said GnRH antagonist is for administration for at least one year.

29. The GnRH antagonist for use according to any one of claims 1 to 28, wherein said GnRH antagonist is for administration multiple times.

30. The GnRH antagonist for use according to any one of claims 1 to 29, wherein said GnRH antagonist is for administration multiple times per day, daily, weekly, or monthly.

31. The GnRH antagonist for use according to any one of claims 1 to 30, wherein said GnRH antagonist is for administered with a single loading dose followed by a lower maintenance dose administered multiple times per day, daily, weekly, or monthly.

32. The GnRH antagonist for use according to any one of claims 1 to 31, wherein the GnRH antagonist is a long-acting GnRH antagonist or is in the form of a sustained release preparation and is for administration at an initial loading dose of 20 to 1000 mg, e.g. 240 mg, followed by a maintenance dose of either (i) 60 to 1000 mg, e.g. 80-160 mg, every 2 weeks, or (ii) 30 to 300 mg, e.g. 40-150 mg, every week.

33. The GnRH antagonist for use according to claim 32, wherein the GnRH antagonist is Degarelix.

34. The GnRH antagonist for use according to any one of claims 1 to 31, wherein the GnRH antagonist is a short-acting peptide GnRH antagonist and is for administration at a dosage of 0.75 to 30 mg/day, administered 1 or more times a day,

35. The GnRH antagonist for use according to claim 34 wherein the GnRH antagonist is for administration at a dosage of 2 to 10 mg/day, preferably 3 to 5 mg/day.

36. The GnRH antagonist for use according to claim 34 or claim 35, wherein the GnRH antagonist is cetrorelix or ganirelix.

37. The GnRH antagonist for use according to any one of claims 1 to 31, wherein the GnRH antagonist is a small molecule orally administrable non-peptide GnRH antagonist and is for administration at a dosage of 0.1 to 3000 mg/day, administered 1 or more times a day.

38. The GnRH antagonist for use according to claim 37, wherein the GnRH antagonist is relugolix, elagolix, ASP1707 or a spiroindoline derivative or a pyrrole, pyrazole, pyridinone, pyrimidinone, pyrrolidine, imidazole, imidazoline, quinolinone, quinoline, quinazonline, indole, furamide, oxazole, triazine-triole, pyrazinone, thiazole, or carbazole derivative.

39. The GnRH antagonist for use according to any one of claims 34 to 38, wherein the GnRH antagonist is for administration at least 2, 3, 4 or 5 times a day, for example 3 to 6 times a day.

40. A product comprising a GnRH antagonist and an additional active agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of an inflammatory condition in a subject, selected from an inflammatory disease, chronic inflammation, age-related inflammation or inflammatory peripheral GnRH, wherein said additional agent is useful in the treatment of said inflammatory condition, and wherein said GnRH antagonist and additional active agent are for long-term administration to said subject for a period of at least 12 weeks.

41. The product of claim 40, wherein said additional active agent is as defined in any one of claims 20 to 25 and/or wherein the GnRH antagonist is as defined in any one of claims 17, 18 or 26 to 39 and/or wherein the the inflammatory condition is as defined in any one of claims 2 to 16.

42. A method of treating or preventing an inflammatory condition in a subject, selected from an inflammatory disease, chronic inflammation, age-related inflammation or inflammatory peripheral GnRH, said method comprising:

administering a GnRH antagonist to said subject, wherein said GnRH antagonist is administered long-term to said subject for a period of at least 12 weeks.

43. The method of claim 42, wherein said inflammatory condition is as defined in any one of claims 2 to 16.

44. The method of claim 42 or claim 43, wherein said GnRH antagonist is as defined in any one of claims 17, 18 or 26.

45. The method of any one of claims 42 to 44, wherein said GnRH antagonist is administered as defined in any one of claims 27 to 39.

46. The method of any one of claims 42 to 45, further comprising the step of administering one or more additional active agents.

47. A method of treating or preventing an inflammatory condition in a subject, selected from an inflammatory disease, chronic inflammation, age-related inflammation or inflammatory peripheral GnRH, said method comprising:

administering a combination of a GnRH antagonist and an additional active agent for treatment of said condition to said subject, wherein said GnRH antagonist and said additional active agent are administered long-term to said subject for a period of at least 12 weeks.

48. The method of claim 46 or claim 47, wherein said additional active agents are as defined in any one of claims 20 to 25.

49. The method of claim 47 or claim 48, wherein the GnRH antagonist is as defined in any one of claims 17, 18 or 26, and/or wherein said GnRH antagonist is administered as defined in any one of claims 27 to 39 and/or wherein the the inflammatory condition is as defined in any one of claims 2 to 16.

50. Use of a GnRH antagonist as defined in any one of claims 1, 17, 18 or 26 for the manufacture of a medicament for use in the treatment or prevention of an inflammatory condition in a subject, selected from an inflammatory disease, chronic inflammation, age-related inflammation or inflammatory peripheral GnRH as defined in one claims 1 to 16, wherein said GnRH antagonist is for long-term administration to said subject for a period of at least 12 weeks and said administration is as defined in any one of claims 1 or 27 to 39.

51. A conjugate comprising a GnRH antagonist linked to a polymer which serves to inhibit passage of the GnRH antagonist across the blood brain barrier.

52. A pharmaceutical composition comprising a conjugate as defined in claim 51, together with at least one pharmaceutically acceptable carrier or excipient.

53. The GnRH antagonist for use according to any one of claims 1 or 15 to 30, or the method according to any one of claims 42 to 48, for treating inflammatory peripheral GnRH, wherein the level of peripheral GnRH in a subject is determined prior to administration of the antagonist, or is monitored over a period of time, prior to and/or during administration of the GnRH antagonist.

54. The GnRH antagonist for use or the method according to claim 53, wherein the GnRH antagonist is administered if the level of peripheral GnRH is 300pg/ml or above.

55. A method for detecting or determining an inflammatory condition in a subject, said method comprising determining the level of peripheral GnRH in said subject.

56. The method of claim 55, wherein said method is carried out on a sample of tissue or body fluid of said subject.

57. An agent capable of disclosing peripheral GnRH level and/or activity for use in diagnosing an inflammatory condition in a subject.