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(54) Title: METHOD OF TREATMENT OF CHRONIC NONBACTERIAL PROSTATITIS WITH SELECTIVE ESTROGEN RECEPTOR MODULATORS OR AROMATASE INHIBITORS

(57) Abstract: A method for treatment or prevention of chronic nonbacterial prostatitis in individuals without urethral sphincter dysfunction, comprises administering an effective amount of (i) a selective estrogen receptor modulator (SERM) having estrogen antagonist effect in the prostate, (ii) an aromatase inhibitor, and/or (iii) an antiestrogen.



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TITLE

**METHOD OF TREATMENT OF CHRONIC NONBACTERIAL
PROSTATITIS WITH SELECTIVE ESTROGEN RECEPTOR
MODULATORS OR AROMATASE INHIBITORS**

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention is directed to a method of treating men suffering from chronic nonbacterial prostatitis with a selective estrogen receptor modulator (SERM) compound, an aromatase inhibitor and/or an antiestrogen.

DESCRIPTION OF RELATED ART

[0002] Prostatitis is an inflammatory disorder of the prostate, which close to 50 percent of all men suffer at some stage of their life. Chronic nonbacterial prostatitis involves inflammation of the prostate gland and commonly affects men of all ages. It can cause chronic pelvic pain syndrome (CPPS), problems urinating, including discomfort and pain, increased frequency and urge, or problems emptying the bladder.

[0003] In a suitable hormonal milieu, with androgens present, chronic nonbacterial prostatitis may progress to prostate overgrowth (benign prostatic hyperplasia ("BPH")), and to prostate cancer.

[0004] Selective estrogen receptor modulators ("SERMs") are compounds binding to estrogen receptors in different tissues but exercising either antagonistic

or agonistic effects. Compounds like tamoxifen, toremifene, raloxifene, lasofoxifene, bazedoxifene, ospemifene and fispemifene are typical SERMs. They share some common characteristics such as being antiestrogenic in breast cancer and estrogenic in bone, whereas in other organs they show varying degrees of estrogenic or antiestrogenic properties. In the urinary tract, the antiestrogenic properties seem to prevail.

[0005] Experimental models have shown that selective estrogen receptor modulators (SERMs) may be useful for treating or preventing lower urinary tract symptoms (LUTS). A method for the treatment or prevention of lower urinary tract symptoms, including nonbacterial prostatitis, with SERMs is fully disclosed in U.S. Patent Application No. 10/454,823, incorporated herein by reference.

[0006] U.S. Patent No. 5,972,921, incorporated herein by reference, teaches treatment of urethral sphincter dysfunction, which causes LUTS by aromatase inhibitors.

[0007] The basis for treating urinary tract symptoms with SERMs or aromatase inhibitors is the observation that an increase of the ratio of estradiol to testosterone results in the development of urethral sphincter dysfunction, which causes LUTS. However, although chronic nonbacterial prostatitis with pelvic pain may sometimes be associated with urethral sphincter dysfunction, the cause of chronic nonbacterial prostatitis has not previously been shown to be estrogen dependent.

[0008] In men, obstruction of the urethra by benign prostatic hyperplasia (BPH), a benign enlargement of the prostate, is frequently considered to be the major cause of LUTS. However, several studies have shown that there is only a weak correlation between prostate enlargement, obstruction and LUTS.

SUMMARY OF THE INVENTION

[0009] It has now been found that chronic nonbacterial prostatitis is estrogen dependent. Increased estrogen to androgen concentration ratio in adult Noble rats causes nonbacterial prostatitis as a direct effect in the prostate without simultaneous urethral sphincter dysfunction. Prostatitis in rats is determined by

observation of inflammatory cells, and the histology has been found to be similar to that in men.

[0010] Consequently, the present invention is a method of treating chronic nonbacterial prostatitis in men, wherein the chronic nonbacterial prostatitis is not associated with urethral sphincter dysfunction. The method comprises administering an effective amount of (i) a selective estrogen receptor modulator having antiestrogenic effect in the prostate, (ii) an aromatase inhibitor, and/or (iii) an anti-estrogen, to a patient in need thereof.

[0011] The invention is also a method of preventing the progression of BPH and, prostate cancer. Development of stromal overgrowth (homologous to stromal overgrowth in human BPH) and development of prostate cancer are associated with long term duration of chronic prostatitis. Treating the chronic prostatitis with SERMs, e.g. fispemifene, or aromatase inhibitors or antiestrogen, will prevent progression of BPH or development of prostate cancer.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The inventors have found that SERMs, such as fispemifene, antagonize the estrogen effect in the prostate and may thus be used to prevent or treat chronic nonbacterial prostatitis. Similarly, lowering of estrogen concentration in the body by using aromatase inhibitors, or by using anti-estrogens, can be used to treat this condition.

[0013] To show the influence of increased estrogen to testosterone ratio on chronic nonbacterial prostatitis, a first group of Noble rats were treated for 6 weeks with testosterone (T) (240 ug/day) and estradiol (E2) (70 ug/day), to produce a profile in the animals of normal T/high E2. (Ratio of T/E2 was 30 in the test group compared to 150 in controls; T concentration was 0.8 ng/ml compared to 1.5 in control; E2 concentration 30 pg/ml compared to 10 pg/ml in controls.) The animals exhibited nonbacterial prostatitis in the absence of obstructed voiding, and normal size prostate.

[0014] To show the effects of a higher ratio of estradiol, in a low testosterone milieu, Noble rats were treated for 13 weeks with T (240 ug/d) and E2 (70 ug/d), exhibiting a profile of low T/high E2. (Ratio of T/E2 was 1 to 10 in the test

group, compared to 150 in controls; testosterone concentration was 100 pg/ml compared to 1.5 ng/ml in control; estradiol concentration was 40-80 pg/ml compared to 10 pg/ml in the controls.) The animals in this group exhibited chronic nonbacterial prostatitis, without significant urodynamic changes, and again in the absence of obstructed voiding. The animals exhibited small prostate, but with stromal overgrowth similar to benign prostatic hyperplasia in men.

[0015] To demonstrate the effects of an elevated estradiol-to-testosterone ratio in the context of a high testosterone milieu, a third group of Noble rats was treated for 13 weeks with T (800 ug/d) and E2 (70 ug/d). The ratio of T/E2 was 75 in the test group compared to 150 in controls. Testosterone concentration was 4.5 ng/ml in the test group compared to 1.5 ng/ml in controls. The estradiol concentration was 60 pg/ml compared to 10 pg/ml in the controls). The prostate in these animals was larger than normal, exhibiting chronic prostatitis and precancerous lesions and ductal carcinomas of the prostate, suggestive of a trend toward development of BPH and prostate cancer.

[0016] To demonstrate the use of an estrogen antagonist to treat chronic nonbacterial prostatitis, a fourth group of rats was treated for 3 weeks with T (240 ug/day) and E2 (70 ug/day), and thereafter administered 2 doses of a pure estrogen antagonist fulvestrant (5mg/kg) on the third week. Fulvestrant significantly reduced the prostatitis compared to the control group treated with T and E2 only. As prostatitis can be reversed by administering an antiestrogen, the condition is seen to be estrogen dependent.

[0017] To demonstrate the estrogen antagonist effect of fispemifene in the prostate, a fifth group of Noble rats was castrated and treated for three weeks with fispemifene at doses of 3, 10 and 30 mg/kg, with and without concomitant estradiol administration (70 ug/day). It was observed that fispemifene was an estrogen antagonist in the prostate, and dose dependently inhibited the effect of estradiol on the prostate, measured by FRA2 or PR expression, which are sensitive markers of estrogen effect.

[0018] It is believed that doses of 0.1 to 100 mg / kg of fispemifene (or other SERM) administered to human males by various routes including, without limitation, oral, topical, transdermal, or subcutaneous routes, will have an

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estrogen antagonist effect in the prostate to treat chronic nonbacterial prostatitis and/or prevent the development of BPH and prostate cancer. A preferred dosage range is about 0.1 to about 10.0 mg/kg, with expected daily dosages expected to be in the range of about 100 mg to about 300 mg per person. It is believed the oral administration route is the most preferable. Suitable preparation forms include for example tablets, capsules, granules, powders, suspensions, and syrups.

WHAT IS CLAIMED IS:

1. A method of treating chronic nonbacterial prostatitis in men, comprising administering to a patient in need thereof an effective amount of an agent selected from the group consisting of (i) a selective estrogen receptor modulator having antiestrogen effect in the prostate, (ii) an aromatase inhibitor, (iii) an antiestrogen and combinations thereof.
wherein said chronic nonbacterial prostatitis is not associated with urethral sphincter dysfunction.
2. A method of preventing the progression of benign prostatic hyperplasia (BPH) or prostate cancer in men, comprising administering to a man having chronic nonbacterial prostatitis in the absence of urethral sphincter dysfunction an effective amount of an agent selected from the group consisting of (i) a selective estrogen receptor modulator having anti-estrogen effect in the prostate, (ii) an aromatase inhibitor, (iii) an antiestrogen and combinations thereof, to prevent the progression of estrogen dependent BPH or prostate cancer.
3. The method of claim 1 or 2, comprising the step of administering fispemifene in an amount in a range of about 0.1 to about 100 mg/kg of body weight.