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Review article

Testosterone suppression combined with high dose estrogen as potential treatment of SARS-CoV-2. A mini review

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ABSTRACT

Compared to females, males experience severe acute respiratory syndrome due to COVID-19 (SARS-CoV-2) more often, and also die more frequently from COVID-19. Testosterone has inhibitory and estrogens have favorable effects on the immune system. Both ACE2 and TMPRSS2 are specific host-cellular proteins stimulating viral entry in cells and SARS-CoV-2. Both proteins can be suppressed by inhibition of testosterone levels and by stimulation of estrogen levels. Therefore, both androgen-deprivation therapy (ADT) and estrogen therapy (ET) may decrease COVID-19 virus cell entry. Literature was searched for evidence of COVID-19 treatment benefits with estrogens, progesterone, androgen deprivation, and anti-androgens. Data supporting the effect of ADT on SARS-CoV-2 are sparse and inconsistent. The benefit of anti-androgen therapy is inconsistent. Data on the effect of ET were not found. Indirect estrogen data related to menopausal hormone therapy and hormonal contraception are favorable. In a small study, progesterone had some beneficial effects. The combination of ADT and ET (ADET) has never been studied as a treatment option for SARS-CoV-2. Based on the mode of action of the combination, it is hypothesized that ADET may be an effective and safe treatment of SARS-CoV-2, to be confirmed in a clinical trial.

1. Introduction

The COVID-19 pandemic has urgently increased the need for a treatment of the severe acute respiratory syndrome (SARS), occurring frequently as complication of a COVID-19 infection. Since the development of new drugs is complicated and time-consuming, there is a continuous search for the potential efficacy of already existing drugs with known safety track records. Compounds worth considering for this purpose are the sex hormones androgens, estrogens, and progesterone (P4). In general, sex hormones are powerful biologicals, affecting many genes, biological systems and organs. Moreover, there is a tremendous amount of knowledge about the function, effects, side-effects, and safety of sex hormones which justifies considering them as alternative treatment for serious COVID-19.

Most studies report a higher incidence of serious COVID-19 infections in males compared to females especially at ages above 50 years, which may be due to sex-related immunomodulation (Angelides et al., 2020; Pastor-Barriuso et al., 2020; Peckham et al., 2020). Global health data clearly indicate a higher mortality rate in males compared to females due to the severe acute respiratory syndrome, caused by the coronavirus 2 (SARS-CoV-2), as illustrated in Figure 1 (Hoffmann et al., 2020). In a retrospective analysis of 1764 hospitalized patients, Ferretti et al. showed a higher mortality in males versus females [HR 1.58 (95%CI 1.30, 1.91; $p < 0.001$)], adjusted for age and comorbidities (Ferretti et al., 2022). A meta-analysis of data of over one million COVID-19 patients also showed a higher mortality rate in males versus females [RR 1.60 (95%CI 1.53, 1.68)] (Perez-Lopez et al., 2020). These observations could be associated with the 10–20 times higher testosterone level in males (Giagulli et al., 2021), since testosterone has unfavorable effects on the immune system (Angelides et al., 2020), and also stimulates angiotensin converting enzyme-2 (ACE2) and the androgen-regulated protease transmembrane protease serine 2 (TMPRSS2), which both facilitate the entry of the COVID-19 virus into the cell (Hoffmann et al., 2020). Testosterone suppression by androgen-deprivation therapy (ADT) decreases the effects of ACE2 and TMPRSS2 (Mauvais-Jarvis et al., 2020).

Estrogens have favorable effects on the immune system since these steroids support innate immune inflammatory responses and stimulate B-cell responses and antibody production (Mauvais-Jarvis et al., 2020). Just like ADT, estrogen treatment (ET) has the same beneficial suppressive effect on ACE2 and TMPRSS2 and both ADT and ET have been

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recognized separately as possible treatments for SARS-CoV-2 (Mauvais-Jarvis et al., 2020). Recently, we have suggested to combine both treatments and we hypothesized that Androgen Deprivation (AD) by testosterone suppression combined with high-dose Estrogen Therapy (ET) may be an effective and safe treatment of SARS-CoV-2 (the ADET hypothesis) (Coelingh Bennink et al., 2021a). From the perspective of ADT this is especially relevant, because ADT not only suppresses testosterone, but also estrogens, so the favorable anti-COVID effects of estrogens are lost during ADT, which is restored by the addition of ET. Also estrogen-only treatment of COVID-19 may be more effective when combined with ADT (Li et al., 2020).

In this paper, we review the endocrine effects of sex hormones as well as the ADT and ET studies performed so far in patients with COVID-19, and we propose a study design to test the ADET hypothesis.

2. Methods

We performed a search (PubMed, Google and ClinicalTrials.gov) for studies on the use of hormonal treatments of serious COVID-19, using estrogens, progesterone, androgen-deprivation (by luteinizing hormone-releasing hormone (LHRH) agonists or gonadotropin-releasing hormone (GnRH antagonist)) and anti-androgen therapies (AAT). In addition, we performed additional searches using the combination of COVID-19 and the terms estrogen, progesterone, estradiol and estetrol as hormones; degarelix, relugolix, aberelix, leuprolide and goserelin as LHRH/GnRH analogues and bicalutamide, proxalutamide, enzalutamide, dutasteride and finasteride as anti-androgen therapy (AAT).

In total, 25 studies investigating the effects of these treatment modalities of COVID-19 were found (15 completed, 10 ongoing). Five on the effect of ADT (Table 1), nine on the effect of AAT (Table 2), and 11 on the effect of estrogens or progesterone (Table 3).

3. Results

3.1. COVID-19 and sex hormones in males and females

There is consensus that serious COVID-19 infection is a disease of elderly people with a steeply rising incidence from about 50 years of age onwards. Furthermore, although the incidence of COVID-19 is equal in men and women (Peckham et al., 2020), serious COVID-19 occurs about twice as much in males, and men die at least twice as frequently after age 50 (Figure 1) (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/?explore=country&country=england#search (accessed on December 9, 2021)). Sex differences are also reported, but not explained by Brodin (2021), mentioning that "women elicit stronger type I IFN responses upon stimulation with TLR7 ligands (Berghofer et al., 2006), and develop stronger vaccine responses (Klein et al., 2015), but also more side effects, and have better survival rates for a number of acute infections than do men" (Klein et al., 2010). Li et al. provide a potential explanation of the sex differences by linking the unique location of the ACE2 gene on the X chromosome to the lack of an alternative mechanism for cellular protection in men (Li et al., 2020).

Spini et al. believe that a sex- and gender-related approach is crucial (Spini et al., 2021). Clearly, a better understanding of the reported sex differences may lead to new treatment options for COVID-19. While the reasons are likely to be multifactorial, a potentially relevant difference may be the much higher synthesis and blood levels of testosterone in men. Testosterone levels in males range from 12-35 ng/mL and decrease slowly from about 40 years onwards. Testosterone levels in females with a menstrual cycle range from 1-3 ng/mL and decrease after menopause. The levels of other sex hormones do not differ after the age of 50 in men and women. The menstrual cycle estrogen estradiol (E2) ranges from 20-35 pg/mL and the less potent postmenopausal estrogen estrone (E1) is present at levels between 10-100 pg/mL in both sexes. Progesterone (P4) is only present in significant amounts in women during the luteal phase of the menstrual cycle and during pregnancy.

3.2. COVID-19 and testosterone

Assuming that testosterone is implicated in susceptibility to serious COVID-19 (Giagulli et al., 2021), what is the effect of this hormone on the immune system? In general, androgens are well known to have immune suppressive effects (Ben-Batalla et al., 2020; Sharifi and Ryan 2020; Trigunaite et al., 2015). Testosterone has inhibitory properties on the immune system, both on cytokine production and lymphocyte proliferation (Chedraui and Perez-Lopez 2020). Apart from this general effect of testosterone, there are two specific, testosterone dependent, host cellular proteins, related to viral cell entry and to serious COVID-19 disease. First, the virus uses ACE2 to enter into the host cell (Hoffmann et al., 2020). Second, the viral spike protein is primed by TMPRSS2, which is an androgen-regulated protease and inhibition of TMPRSS2 using a protease inhibitor blocks cell entry of the virus (Hoffmann et al., 2020). Serious COVID-19 is characterized by deterioration of lung function and testosterone stimulated TMPRSS2's expression in the lung may explain the higher susceptibility of men to develop serious COVID-19 lung infections (Montopoli et al., 2020). Androgen sensitivity more than levels may be the critical factor in determining COVID-19 severity (Koskinen et al., 2020; Mohamed et al., 2021).

Suppression of ACE2 and TMPRSS2 by inhibition of testosterone synthesis or direct androgen receptor blockade may be an effective treatment of COVID-19, interfering with viral cell entry or activation (Sharifi and Ryan 2020).

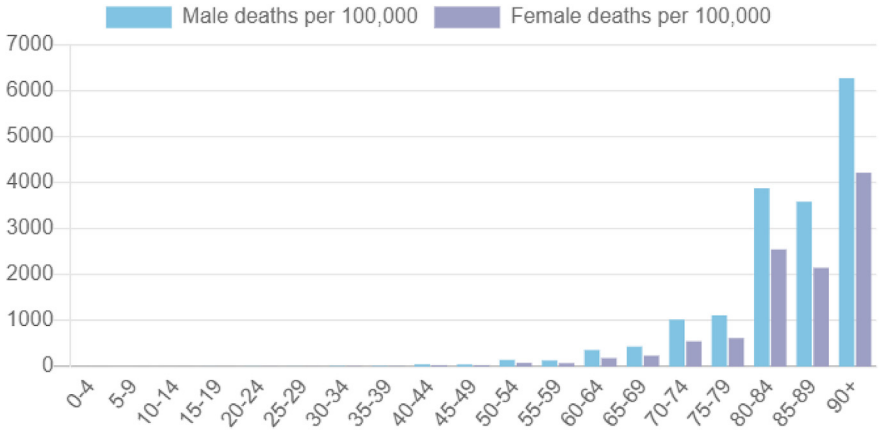

Figure 1. Incidence of male and female deaths by age groups, reported in England during the period 6 May 2020–24 November 2021 (GlobalHealth (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/?explore=country&country=england#search (accessed on December 9, 2021))).

Table 1. Overview of studies investigating the effects on COVID-19 by androgen-deprivation therapy (ADT) by GnRH/LHRH analogues.

Treatment	Status/Outcome	Reference
Cohort of PC patients receiving ADT or AAT	May be considered to reduce SARS-CoV-2 infections or complications in high-risk male populations	(Montopoli et al., 2020) *
Cohort of PC patients receiving ADT or AAT	Results do not support a role for ADT or AAT (no ADT-alone outcome presented)	(Koskinen et al., 2020) (Kwon et al., 2021) (Klein et al., 2021)
Degarelix (HITCH) males >18 yr	Degarelix did not result in amelioration of COVID-19 severity	(Nickols et al., 2022)

AAT: anti-androgen therapy; ADT: androgen-deprivation therapy; GnRH: gonadotropin-releasing hormone; LHRH: luteinizing hormone-releasing hormone.

* Commented by Koskinen (Koskinen et al., 2020), Patel (Patel et al., 2020), Bennani (Bennani and Bennani-Baiti 2020), Zumerle (Zumerle et al., 2020), O'Callaghan (O'Callaghan et al., 2020) and Kwon (Kwon et al., 2021).

Although these unfavorable effects of high testosterone levels on ACE2 and TMPRSS2 are confirmed by Giagulli et al., (2021), and Younis et al., (2021), these authors conclude that not high, but low testosterone levels may predispose to poor prognosis or death due to COVID-19 in men. However, in both papers the fact that low testosterone implicitly also means low estrogen (especially E2) is not mentioned, whereas low estrogens itself may be an unfavorable factor for the prognosis of COVID-19 (see below). Also, instead of relating the low testosterone to the negative outcome, the low testosterone may also reflect the endogenous suppression by the well-known inhibitory effect on this hormone due to the stress of a serious disease. As such, suppression of testosterone is a functional protective effect of the body to limit a factor that interferes with immunological competence, as testosterone does. Still the testosterone levels in men are higher than in women and therefore, in ADET a further decrease of testosterone levels could provide beneficial effect, but only when combined with an increase of estrogens levels since lowering testosterone decreases E2 (Freedland et al., 2009).

There is a clinical situation, where suppression of testosterone is already safely and effectively practiced, which is the treatment of advanced prostate cancer (PC) by ADT. In these patients, sustained testosterone suppression, well below castration level, is obtained by long-term treatment with the gonadotropin-releasing hormone (GnRH) antagonists degarelix or relugolix, and (although delayed or less pronounced) with the luteinizing hormone-releasing hormone (LHRH) agonist leuprolide (Crawford et al., 2011; Shore et al., 2020). Remarkably, separate from its role in viral infections, TMPRSS2 has a widely recognized role in PC pathogenesis, as approximately half of all tumors harbor a TMPRSS2 related translocation and the beneficial effect of ADT in PC may be partially related to the inhibition of TMPRSS2.

There are only a few reports published on the effects of ADT on COVID-19 (Table 1). Montopoli et al. were the first to report that PC patients receiving ADT appear to be partially protected for serious COVID-19 infections (Montopoli et al., 2020), but this has been questioned by others (Klein et al., 2021; Koskinen et al., 2020; Kwon et al., 2021). This controversy may be due to the fact that ADT by suppression of gonadotrophins using GnRH antagonists and agonists is accompanied by strong suppression of estrogens, thereby taking away an important protective anti-COVID factor (Freedland et al., 2009). In line with the above, the recently reported HITCH trial with the GnRH antagonist degarelix in male hospitalized COVID-19 patients did not result in amelioration of COVID-19 severity (Nickols et al., 2022). So far, no anti-COVID-19 studies have been initiated using agonists such as e.g. leuprolide, possibly because the initial flare in testosterone levels is considered prohibitive (Crawford et al., 2019; Shore et al., 2020).

Table 2. Overview of studies investigating the effects on COVID-19 by anti-androgen- therapy (AAT).

Treatment	Status/Outcome	Reference
Nonsteroidal androgen receptor antagonists		
Bicalutamide (plus camostat) in men and women (≥60 yr)	Terminated	NCT04652765
Proxalutamide in men and women (≥18 yr)	Acceleration viral clearance; increased recovery rate; reduced mortality and hospitalization rates	(Cadegiani et al., 2021b) (Cadegiani et al., 2021c)
Proxalutamide in men (≥18 yr)	Reduced hospitalization rate	(McCoy et al., 2021)
Proxalutamide (ICU study); men and women (≥18 yr)	Terminated	NCT04853927
Enzalutamide (preclinical)	Our findings do not support the postulated protective role of enzalutamide in treating COVID-19 through reducing TMPRSS2 expression in lung cells	(Li et al., 2021)
Enzalutamide (preclinical)	Data presented provides strong evidence to support clinical trials to assess the efficacy of antiandrogens as a treatment option for COVID-19	(Leach et al., 2021)
Enzalutamide (COVIDENZA) in men and women (≥50 yr)	No evidence of benefit; study prematurely terminated	(Welen et al., 2022)
5α-Reductase inhibitors		
Dutasteride or finasteride in men (≥18 yr)	Significant lowering of ICU admission	(Goren et al., 2021)
Dutasteride (EAT-DUTA AndroCoV) in male outpatients (≥18 yr)	Reduction viral shedding and inflammatory markers	(Cadegiani et al., 2021a)
Finasteride in men (≥50 yr)	Improves O2 saturation	(Zarehoseinzade et al., 2021)

AAT: anti-androgen therapy.

Another reason for the ambiguous results reported for the ADT studies may be that the cohorts investigated in these studies do not distinguish between the effects of ADT by GnRH antagonists or LHRH agonists, AAT, and/or the combination of ADT and AAT (Cadegiani et al., 2021b). Preliminary data regarding studies investigating the effects of AAT-only on COVID-19 suggest a beneficial effect (Table 2) (Cadegiani et al. 2021a, 2021b; Goren et al., 2021; McCoy et al., 2021; Zarehoseinzade et al., 2021). This may be partly explained by the fact that AAT interferes with testosterone action, but does not suppress testosterone levels, so E2 synthesis is not inhibited, which is advantageous from the anti-COVID perspective. Leach et al. suggest that the effect of AAT on COVID-19 is more prominent than with ADT due to the stronger downregulation of TMPRSS2 (Leach et al., 2021). A study with proxalutamide in 778 male and female patients revealed an increased recovery rate, and reduced mortality and hospitalization rates (Cadegiani et al., 2021c). However, the prematurely terminated COVIDENZA phase 2 study with the anti-androgen enzalutamide showed no benefit (Table 2), supported by epidemiological and *in-vitro* data (Welen et al., 2022).

3.3. COVID-19, estrogens and progesterone

Both estrogens and progesterone have effects on the immune system that could mitigate COVID-19, with special emphasis on inhibition of the cytokine storm, that may complicate the disease (Mauvais-Jarvis et al., 2020; Schust et al., 1996). Both E2 and P4 treatment can blunt innate immune inflammatory responses and at the same time stimulate B-cell responses and antibody production, all expected to have a favorable

Table 3. Overview of studies investigating the effects on COVID-19 by estrogens and progesterone.

Treatment	Status/Outcome	Reference
Oral E2 in postmenopausal women (retrospective study)	Strong positive effect on survival rates	(Seeland et al., 2020)
Oral HRT in postmenopausal women (retrospective cohort study)	HRT was associated with a significantly lower likelihood of all-cause mortality	(Dambha-Miller et al., 2022)
COC or HRT use (COVID Symptom Study)	Findings support a protective effect of estrogen exposure	(Costeira et al., 2021)
HRT use in women (≥60 yr) (EPICOVID19 survey)	Lower probability of having a positive test	(Prinelli et al., 2022)
COC use	Lower impact on coagulation parameters of COCs containing E2 compared to EE	(Lete 2021)
i.m. E2-cypionate and oral P4 in men and women (≥18 yr)	Completed, not reported	NCT04865029 (Lovre et al., 2021)
E2 patch in men (≥18 yr) and women (≥55 yr)	Terminated	NCT04359329
E2 gel in men (≥18 yr) and postmenopausal women	Ongoing	NCT04853069
E2 + P4 patch in men (≥18 yr) and women (≥55 yr)	Ongoing	NCT04539626
Oral E4 in men (≥18 yr) and postmenopausal women	Completed	NCT04801836 (Mithra Pharmaceuticals. https://www.mithra.com/en/mithra-announces-topline-results-for-covid-19-phase-ii-study (accessed on September 27, 2021))
s.c. P4 in men (pilot study)	Effective in hypoxic men with moderate/severe COVID	(Ghandehari et al., 2021)

COC: combined oral contraception; E2: estradiol; E4: estetrol; EE: ethinylestradiol; HRT: hormone replacement therapy; P4: progesterone.

effect on the course of COVID-19 (Mauvais-Jarvis et al., 2020). In contrast to testosterone, E2 reduces the expression of ACE2 and the activity of TMPRSS2, thereby inhibiting viral cell entry and increasing viral clearance in women who have significant levels of estrogens (Chedraui and Perez-Lopez 2020).

Experimental studies have shown that male mice are highly susceptible to SARS-CoV infection compared to age-matched females. Increased numbers of neutrophils and Inflammatory Monocytes Macrophages (IMMs) were counted in lungs of SARS-CoV–infected males. Additionally, increased numbers of IMMs correlated with elevated levels of proinflammatory cytokines and chemokines in the lungs of male mice, and these cells also produced more of these inflammatory mediators in male mice compared with female mice (Channappanavar et al., 2017). Gonadectomy or treatment with flutamide, a nonsteroidal anti-androgen, did not reduce morbidity and mortality in male mice, suggesting that in mice, androgens do not play a major role in SARS-CoV pathogenesis. In marked contrast, ovariectomized SARS-CoV infected female mice showed progressive weight loss and 85% had died by day 8, whereas only 10–20% mortality was observed in control female mice. Furthermore, female mice treated with the estrogen receptor antagonist fulvestrant or with the selective estrogen receptor modulator (SERM) tamoxifen were more susceptible to SARS-CoV infection. This enhanced susceptibility of ovariectomized and estrogen receptor antagonist–treated female mice demonstrates the protective effect of estrogen receptor signaling in female animals to COVID-19 infection.

The favorable effects of estrogens in relation to COVID-19 have been summarized recently by Lete (2021), and were observed retrospectively by Seeland (Table 3) (Seeland et al., 2020). This was confirmed in the COVID Symptoms Study in 295,689 women receiving a combined oral contraceptive (COC) and 151,193 women on hormone replacement therapy (HRT), supporting the protective effect of estrogen exposure on COVID-19 (Costeira et al., 2021). Recently, in a population of 1,863,478 women aged over 18 years, a significantly lower likelihood of all-cause mortality in COVID-19 has been reported in postmenopausal women using hormone replacement therapy, suggesting a strong protective effect of estrogens combined with progestins (adjusted OR 0.22; 95% CI 0.05 to 0.94) (Dambha-Miller et al., 2022). These considerations have led to the initiation of clinical studies in male and female patients with COVID-19, investigating the effects of intramuscular or transdermal E2, or oral treatment with the natural estrogen estetrol (E4) (Table 3). In the E4 study in hospitalized men or post-menopausal women suffering from moderate COVID-19, the use of low-dose E4 (15 mg per day) was safe, but results did not differ from placebo in the primary efficacy endpoint related to the severity of COVID-19 (Mithra Pharmaceuticals. https://www.mithra.com/en/mithra-announces-topline-results-for-covid-19-phase-ii-study (accessed on September 27, 2021)). However, anti-estrogen therapy in female cancer patients was related to more severe COVID-19, supporting a possible favorable effect of estrogens (Montopoli et al., 2021). A pilot study with subcutaneous P4 suggested effectiveness in hypoxic men with moderate or severe COVID-19 (Ghandehari et al., 2021).

4. Hypothesis

4.1. Proposal

We propose to investigate the efficacy and safety of a combination of testosterone suppression and a high dose of an estrogen for the treatment of serious COVID-19 disease (ADET). We recently used this combination in a phase II study for the treatment of advanced, locally infiltrating or metastatic, castration-sensitive PC (ClinicalTrials.gov NCT03361969 (Coelingh Bennink, 2021b). In this double-blind, randomized, placebo-controlled study (PCombi) we compared the use of ADT with LHRH agonists with or without co-treatment with the natural estrogen E4 (Coelingh Bennink et al., 2021b). We used E4, since this fetal estrogen has been shown to carry a lower risk of cardiovascular (CV) adverse events compared to other natural or synthetic estrogens (Coelingh Bennink et al., 2017; Douxfils, 2020). In the group receiving 40 mg E4 as co-treatment [high dose estetrol (HDE4)], we found strong estrogen effects, associated with virtual elimination of ADT-induced hot flushes and bone loss. Although the group sizes were limited (41 on HDE4 and 21 on placebo), these differences were statistically significant. In addition, with HDE4 co-treatment, follicle-stimulation hormone (FSH) levels were significantly reduced by 98% vs. 57% on placebo (Coelingh Bennink, 2021b). This is relevant for COVID-19 treatment in aging persons, because both aging males and postmenopausal females have high FSH levels and there is increasing awareness, that suppression of FSH is related to a decreased risk of CV complications (Crawford and Schally 2020). Since COVID-19 is often complicated by coagulation abnormalities and CV adverse events and because low testosterone may increase the risk of thrombosis (Giagulli et al., 2021), concomitant anti-coagulant treatment, if not used already, may be advisable with ADET.

Although ADT may not protect against the occurrence of SARS-CoV-2 infection (Klein et al., 2021; Mohamed et al., 2021; Moradi et al., 2020), it may decrease its severity with lower rates of hospitalization and oxygen requirement (Bennani and Bennani-Baiti 2020; Patel et al., 2020). Very importantly, the proposed ADET co-treatment should not use LHRH agonists, but a GnRH antagonist for ADT, since LHRH agonists increase testosterone levels during the first weeks of treatment (the LHRH agonist testosterone flare) (Crawford et al., 2019; Shore et al., 2020), whereas a

GnRH antagonist will decrease testosterone immediately (Crawford et al., 2011; Shore et al., 2020). The effect of anti-androgens is conflicting (Cadegiani et al., 2021c; Welen et al., 2022), possibly because these compounds do not decrease testosterone levels. The preferred estrogen formulation for ADET is the E2 patch (Langley et al. 2013, 2021), to avoid oral treatment and the first-pass liver effects of estrogens, related to hemostatic changes and an increased risk of CV side effects. Alternatively a high dose of the fetal estrogen E4 as reported for the treatment of advanced PC may be used, since E4 has limited interference with liver function during oral use (Coelingh Bennink et al., 2017; Douxfils, 2020; Mawet et al., 2015). ADET is preferably tested first in older men with serious clinical lung disease.

4.2. ADET COVID hypothesis

We hypothesize that Androgen Deprivation (AD) by testosterone suppression, combined with high-dose Estrogen Therapy (ET), may be an effective and safe treatment of SARS-CoV-2 in men and in women (the ADET hypothesis).

4.3. Testing the ADET COVID hypothesis

We propose a clinical study in patients admitted to an intensive care unit (ICU) because of SARS-CoV-2. Patients should be randomized to either no additional treatment or to co-treatment with GnRH antagonist degarelix injections in a starting dose of 240 mg, combined with transdermal estradiol (E2) patches in a dose of 100 μg/24 h. In general, avoiding oral administration in seriously ill patients is recommended, but alternative oral medications such as the new GnRH antagonist relugolix and a high dose of the natural estrogen estetrol (HDE4) could be used. All patients in the study should receive anti-coagulant treatment. Proposed co-primary endpoints are death and duration of stay at the ICU.

5. Conclusion

Testosterone reduction by combined androgen-deprivation and estrogen therapy (ADET) has never been studied. Based on the mode of action of the combination, we hypothesize that ADET may be an effective and safe treatment of SARS-CoV-2. We propose to test this hypothesis in a clinical trial.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare the following conflict of interests:

Dr. Coelingh Bennink is president and shareholder of Pantarhei Oncology, an affiliate of Pantarhei Bioscience BV, Zeist, The Netherlands. He has submitted a patent application for the ADET treatment concept. Mr Egberts declares no conflict of interest. Dr Debruyne is Medical Director of Andros Men's Health Institutes, the Netherlands, and is consultant for Pantarhei Oncology BV, the company developing ADET for the treatment of advanced prostate cancer.

Additional information

No additional information is available for this paper.

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