Proxalutamide (GT0918) Reduces the Rate of Hospitalization and Death in COVID-19 Male Patients: A Randomized Double-Blinded Placebo-Controlled Trial

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Abbreviations:

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TMPRSS2: Transmembrane protease, serine 2
AGA: Androgenetic alopecia

Key Points

Question: Are anti-androgens effective treatment for COVID-19 in men?

Findings: In a randomized, placebo-controlled, double-blinded, prospective study of 214 men with ambulatory mild COVID-19 disease (WHO ordinal scale ≤3), the rate of hospitalization was significantly lower in men treated with proxalutamide compared to standard of care. 27% of men in the control group required hospitalization versus 0% in the proxalutamide group ($p < 0.001$).

Meaning: Anti-androgens are an effective treatment for men with mild COVID-19 disease.

Abstract

Importance: Previously, we have reported a retrospective cohort analysis demonstrating the protective effect of anti-androgens (5-alpha-reductase inhibitors) in COVID-19.

Objective: To determine if the anti-androgen proxalutimide is an effective treatment for men with ambulatory mild COVID-19 disease.

Design: A double-blinded, randomized, prospective, investigational study of proxalutamide for the treatment men with ambulatory mild COVID-19 disease.

Setting: Outpatient centers (Brasilia, Brazil) from July 15 to December 1, 2020.

Participants: Men with ambulatory mild COVID-19 disease (WHO ordinal scale ≤3).

Interventions: Proxalutimide 200mg/day, or standard of care for 30 days or until full COVID-19 remission.

Main Outcome and Measures: Percentage of subjects hospitalized due to COVID-19 [Time Frame: 30 days].

Results: A total of 214 men were included and completed the trial; 114 men were randomized to the proxalutamide group, and 100 men were randomized to the control group. A statistically significant reduction in the percentage of subjects hospitalized due to COVID-19 was observed in men taking proxalutamide (0%) compared to the standard of care (27%), ($p<0.001$). The percentage of men requiring mechanical ventilation was reduced in the proxalutamide group (0%) compared to control (9%), ($p<0.001$). Zero fatalities occurred in the proxalutamide group, versus 2 in the control group.

Conclusions and Relevance: Men with ambulatory mild COVID-19 disease (WHO ordinal scale ≤3) receiving anti-androgen treatment with proxalutamide, had significantly reduced rate of hospitalization compared to men not receiving anti-androgen treatment.

Trial Registration: NCT04446429

Introduction

Early in the COVID-19 pandemic, reports from Wuhan, China demonstrated that the infectivity and severity of the disease disproportionately affects men. Of patients sampled in the early stages of the outbreak 42% were female versus 58% male.[1] Now that the disease has progressed to the majority of countries across the globe, the trend has been demonstrated many times over; men are more likely to be infected, more likely to have severe disease, and have a greater case fatality rate compared to women.[2] Lifestyle differences and gender-biased comorbidities, e.g., incidence of smoking and hypertension, have been suggested as contributing to this gender discrepancy,[2] however, definitive proof of these associations is lacking. We have previously published several manuscripts suggesting that the male bias in COVID-19 disease severity may be linked to androgens.[3,4]

SARS-CoV-2 entry into type II pneumocytes is dependent on modification of a viral spike protein by the transmembrane protease, serine 2 (TMPRSS2) expressed on the surface of human cells.[5] The only known promoter of the TMPRSS2 gene in humans is an androgen response element located in the 5' promoter region.[6] It would follow that reducing the expression of TMPRSS2 by blocking the androgen receptor would decrease SARS-CoV-2 entry into human cells. Recently, we have published several observation studies linking the androgen-mediated phenotype of androgenetic alopecia (AGA) to COVID-19 disease severity.[3,4] In a cohort of 122 men hospitalized with COVID-19, 79% were diagnosed with AGA compared to the expected prevalence of 31-53% in aged matched controls of similar ethnicity.[3] Additionally, a recent publication has demonstrated that COVID-19 disease severity

was directly correlated with AGA progression; men with higher Hamilton-Norwood stages were more likely to experience severe disease and death.[7]

Further evidence connecting COVID-19 to androgens has been reported in prostate cancer patients undergoing androgen depravation therapy (ADT). Montopoli et al. studied a large population of COVID-19 patients in northern Italy, observing that COVID-19 infection rates were lower in prostate cancer patients receiving ADT compared to prostate cancer patients not receiving ADT (OR 4.05; 95% CI 1.55-10.59).[8] Other groups have suggested that polycystic ovary syndrome may also indicated increase risk of severe COVID-19 disease in women,[9] and a recent study supported this hypothesis.[10] Finally, we have communicated that variations in the androgen receptor gene may contribute to the racial variations in case fatality rates observed in the United States.[11] Taken together, there is growing body of evidence to support that SARS-CoV-2 infectivity is mediated by the androgen receptor and may respond to drugs that reduce androgen receptor function.

5-alpha-reductase inhibitors (5ARis) are commonly prescribed for androgenetic alopecia and benign prostatic hyperplasia; they block the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT).[12] As such, they would make ideal candidates for a SARS-CoV-2 treatment. Recently, we have reported the results from two retrospective cohort analysis demonstrating the protective effect of 5-alpha-reductase inhibitors (5ARi) for men with COVID-19.[13] In a study of 77 men hospitalized with COVID-19 we found among men taking 5ARis, 8% were admitted to the ICU compared to 58% of men not taking 5ARis (P = 0.0015). In the cohort, 5ARis were associated with reduced risk for ICU admissions RR 0.14 (95%

CI: 0.02–0.94).[13] Similarly, we have demonstrated that the frequency of COVID-19 symptoms was drastically reduced for men using 5ARis in an outpatient setting. A statistically significant ($p<0.05$) reduction in the frequency of 20 of the 29 clinical symptoms was observed in AGA men using 5ARis compared to AGA men not using 5ARis. For example, 38% and 2% of men presented with low-grade fever, 60% and 6% with dry cough, and 88% and 15% reported anosmia in the non-5ARi and 5ARi groups, respectively.[14]

One limitation of 5ARis is the time course required to achieve systemic DHT reductions. As such, we explored the use of a novel second generation androgen receptor antagonist proxalutamide as a means for rapid reduction in AR activity. Proxalutamide (GT0918) demonstrates a dual mechanism of action. It is highly effective in inhibiting AR as well as exhibiting pharmacological effects of inducing the down-regulation of AR expression; the mechanism that is not present in bicalutamide and enzalutamide. Because of the dual mechanism of action, it is expected to be a more effective and less toxic second-generation anti-androgen drug therapy. Clinical evidence has demonstrated that proxalutamide lowers AR expression and activity. Additionally, it has been reported that Proxalutamide lowers the expression of ACE2. Both would be beneficial for preventing SARS-CoV-2 entry into lung cells.

Methods

Study Design and Oversight

Potential male subjects were recruited to a double-blinded, randomized, placebo-controlled, prospective, interventional study of anti-androgen treatment for COVID-19 (NCT04446429). Prospective subjects for the study presented with mild COVID-19 disease (WHO ordinal scale ≤3) to outpatient centers (Centro Clínico Advance and Exame Imagem e Laboratorio, Brasilia, Brazil). The study was registered (clinicaltrial.gov) and conducted with the approval of the Brazilian National Ethics Committee: #4.173.074; process number (CAAE) 34110420.2.0000.0008; Comitê de Ética em Pesquisa (CEP), Comitê Nacional de Ética em Pesquisa (CONEP), Ministry of Health (Ministério da Saúde (MS)) (CEP/CONEP/MS). All patients admitted to the study gave informed consent.

Baseline characteristics, comorbidities, test results, and medications used were extracted from patient records. For each subject, the age, BMI (kg/m^2), frequency and duration of medication used and the following pre-existing conditions were extracted from records: type 2 diabetes, hypertension, obesity (BMI), hypothyroidism, hypogonadism, androgenetic alopecia, asthma, and chronic obstructive pulmonary disease (COPD). Data were extracted by the principal investigator and managed by the study director.

Study Population and Covariates

Men being screened for inclusion in the study were recruited through social media as well as a mailing list of 10,900 men from the Brazilian health care system

registry. Screening of potential subjects was conducted at two outpatient centers (Centro Clínico Advance and Exame Imagem e Laboratorio Brasilia, Brazil) at which nasopharyngeal swabs were collected by trained medical personal. SARS-CoV-2 status was laboratory confirmed by real-time reverse transcription polymerase reaction testing (Automatized Platform, Roche, USA) following the Cobas SARS-CoV-2 rtPCR kit test protocol.

Procedures

Patients were randomized to receive either proxalutamide or the standard of care. The study was double-blinded, the identification of the group assignment was known only to the study monitor. The randomization plan was based on a 1:1 ratio. The first ten subjects were assigned to group 1, and the second ten subjects were assigned to group 2, etc., until the completion of enrollment. Proxalutamide and placebo pills were manufactured to appear identical (Kintor Pharmecutical Ltd. Suzhou, China). Proxalutamide was given at 200 mg/day for 15 days. For all subjects, standard of care consisted of 500 mg nitazoxanide twice a day for six days and 500 mg azithromycin once a day for five days.

Study Outcomes

Endpoints for the study were percentage of subjects hospitalized due to COVID-19 and the WHO COVID Ordinal Scale defined as: 7. Death, 6. hospitalized on invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation), 5. hospitalized on non-invasive ventilation or high flow nasal cannula, 4. hospitalized on supplemental oxygen, 3. hospitalized not on supplemental oxygen, 2. Not

hospitalized with limitation in activity (continued symptoms), 1. Not hospitalized without limitation in activity (no symptoms).

Statistical Analysis

Sample size estimate was based on a report by Riccardo et al[15] that in Italy the hospitalization rate was as high as 20% among adults above the age of 65 tested positive for SARS-CoV-2. Further, Montopoli et al[8] reported that males represent 60% of hospitalized patients; therefore, we can estimate that the rate of hospitalization of males over the age of 65% tested positive for SARS-CoV-2 is approximately 30%. To estimate the efficacy of proxalutamide as a treatment for COVID-19, we used the 50% reduction in the rate of hospitalization among patients taking androgen depravation therapy reported by Montopoli et al[8]. The statistical method employed to analyze the data was the Chi-squared test for independent proportions. Statistical significance was set at $p<0.05$. XLSTAT version 2020.3.1.1008 (Addinsoft, Inc.) was used to perform all statistical analysis.

Results

Two hundred and fourteen men were included in the trial. 114 men were assigned to the proxalutamide group and 100 men were assigned to the control group. Baseline characteristics of the two study groups were similar.

Twenty seven subjects were hospitalized in the control group compared to zero in the proxalutamide group. Nine subjects required mechanical ventilation in the control group compared to zero in the proxalutamide group. The proportion of COVID-19 patients hospitalized was significantly different between the proxalutamide and control arms; $\chi 2$ (1) = 35.025, $p<.0001$. The difference in proportions was 26.99% with a 95% CI: [8.5981%, 36.4231%]; The data is summarized in **Table 1**. A statistically significant difference in the percentage of subjects requiring for mechanical ventilation ($p<0.001$) was observed in men taking proxalutamide compared to men in the control group. No patient receiving proxalutamide died compared to 2% in the control group. There was no treatment related adverse event during the course of the study.

Discussion

Men infected with SARS-CoV-2 have an increased risk of severe COVID-19 disease compared to women.[2] A multitude of factors may contribute to the gender disparity,[2] however, evidence is mounting[3,4,7,8] to support that androgens, the defining male hormones, may be involved in the regulation of COVID-19 disease severity. Concurrently, the mechanism of action is likely androgen receptor regulation of the expression of the TMPRSS2 enzyme, one of the enzymes utilized by SARS-CoV-2 to enter type II pneumocytes in human lungs.[5]

Androgens are both circulating and produced in tissue. Elevated tissue DHT is implicated in androgenetic alopecia (AGA), benign prostatic hyperplasia, and prostate cancer. It is important to distinguish that the level of tissue DHT is more important than the total level of circulating testosterone. If fact, the use of 5ARis will block the

conversion of testosterone to DHT and may increase overall testosterone. However, DHT is a more potent androgen, hence lowering DHT lowers the overall effect of the androgens, i.e., activation of the androgen receptor, even in the presence of increase testosterone. In a previous communication, we reported that in a cohort of 122 hospitalized COVID-19 male patients, 79% suffered from androgenetic alopecia.[3] Similarly, Montopoli et al.,[8] observed that men utilizing ADT for prostate cancer were less likely to suffer severe COVID-19 disease. These observations led us to study the effect of anti-androgen therapy on COVID-19 outcomes.

Here we demonstrate in a randomized, double-blinded, placebo controlled, interventional study that men treated with proxalutamide, a novel second generation androgen receptor antagonist experience a significantly lower rate of hospitalization ($p<0.001$) and requirement for mechanical ventilation compared to the standard of care.

Conclusion

In men with ambulatory mild COVID-19 disease (WHO ordinal scale ≤3), the novel anti-androgen, proxalutamide (GT0918) demonstrated a significant reduction in the rate of hospitalization as well as the requirement for mechanical ventilation. Due to the encouraging findings of this study, we are conducting a larger study in men hospitalized with moderate COVID-19 disease (WHO ordinal scale 4 or 5).

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Conflict of interest statement

Authors declare no conflict of interest with any of the pharmacological interventions proposed by the present study.

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	Placebo (n=100)	Proxalutimide (n=114)	p
Hospitalization	27 (27.0%)	0 (0%)	<0.001
Mechanical Ventilation	9 (9.0%)	0 (0%)	<0.001
Death	2 (2.0%)	0 (0%)	0.13

Table 1. Clinical outcomes of COVID-19 men treated with Proxalutimide compared to standard of care.