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## **5-Alpha-Reductase Inhibitors are Associated with Reduced Frequency of COVID-19 Symptoms in Males with Androgenetic Alopecia**

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5ARi: 5-alpha reductase inhibitors

AGA: Androgenetic alopecia

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**Dear Editor,** We have previously reported that men with androgenetic alopecia (AGA) are more likely to present with severe COVID-19 symptoms, potentially implicating androgen sensitivity as a risk factor for COVID-19.<sup>1-3</sup> As such, we hypothesized that 5-alpha-reductase inhibitors (5ARi) may reduce the severity of COVID-19 disease. To test this hypothesis we conducted a retrospective cohort analysis on male subjects with laboratory confirmed SARS-CoV-2 infection. The subjects presented at one of five outpatient clinics (Corpometria Institute Brasilia, Brazil) from June 15 to July 28, 2020. At the time of visit, 29 clinical symptoms associated with SARS-CoV-2 infection were documented. For analysis, male subjects with AGA were selected. The frequency of clinical symptoms in males with AGA using 5ARis was compared to those not using 5ARis.

Among the men presenting at the clinic, 300 were positive for SARS-CoV-2. Of these, 65 had AGA but were not using 5ARis, and 48 had AGA and were taking a 5ARi for at least six months prior to the study. The only 5ARi used in this cohort was dutasteride (0.5 mg) for the treatment of AGA. Propensity score matching analysis was performed on the 65 men in the AGA group not using 5ARis to produce a comparator to the 5ARi group (Area under the ROC curve = 0.548). The baseline characteristics of the matched study groups are displayed in **Table I**. The Fisher exact test was used to compare the proportions of clinical symptoms between COVID-19 patients with AGA using 5ARis and not using 5ARis. XLSTAT version 2020.3.1.1008 (Addinsoft, Inc.) was used to perform all statistical analysis.

A statistically significant ( $p < 0.05$ ) reduction in the frequency of 20 of the 29 clinical symptoms was observed in males with AGA using 5ARis compared to males with AGA not using 5ARis (**Figure I**); 5 of the symptoms were indistinguishable ( $p = 1.00$ ) because there were zero or close to zero occurrences in both groups. The largest percent reductions were found in the frequency of anosmia (73%), ageusia (63%), headache (42%), and dry cough (56%).

Men infected with SARS-CoV-2 have an increased risk of severe COVID-19 disease compared to women.<sup>4</sup> A multitude of factors may contribute to this gender disparity,<sup>4</sup> however, evidence is mounting<sup>1-3,5</sup> to support that androgens, the defining male hormones, may be implicated in COVID-19 disease severity. Androgens are both circulating and produced in tissue. Elevated tissue DHT is implicated in AGA, benign prostatic hyperplasia, and prostate cancer. In a previous communication, we reported that in a cohort of 122 hospitalized COVID-19 male patients, 79% suffered from AGA.<sup>1</sup> Similarly, Montopoli et al.,<sup>5</sup> observed that men utilizing androgen deprivation therapy for prostate cancer were less likely to suffer severe COVID-19 disease.

Here we demonstrate that men using the 5ARis, commonly used to treat AGA and benign prostatic hyperplasia, display drastically reduced symptoms of COVID-19 disease in an outpatient setting. It is still unknown if treatment with 5ARis after SARS-CoV-2 infection will be beneficial to male patients. 5ARis, for example, dutasteride, may require days or weeks to lower DHT significantly to produce a

therapeutic effect.<sup>6</sup> These questions have encouraged a larger interventional study of anti-androgens in COVID-19 patients. We are currently conducting a randomized, double-blinded, placebo controlled interventional study with 5ARis (dutasteride) as well as a novel anti-androgen (proxalutamide) in the treatment of COVID-19 (NCT04446429).

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		All SARS-CoV-2 Positive	
		5ARi (n=48)	no 5ARi (n=48)
GROUP-DETERMINING DATA, No.(%)	Androgenetic alopecia	48 (100)	48 (100)
	Dutasteride use	48 (100)	0 (0)
BASELINE DATA, No.(%)	Average Age, No.(SD)	45.6 (12)	45.7 (9)
	BMI > 30 Kg/m <sup>2</sup>	9 (19)	8 (17)
	Hypertension	12 (25)	11 (23)
	Myocardial infarction	2 (4)	2 (4)
	Stroke	0 (0)	0 (0)
	Heart Failure	0 (0)	0 (0)
	Lipid Disorder	24 (50)	17 (35)
	Diabeties	9 (19)	5 (10)
	Pre-diabeties	3 (6)	1 (2)
	Obesity	9 (19)	8 (17)
	Asthma	2 (4)	5 (10)
	COPD	0 (0)	0 (0)
	Cancer (current)	0 (0)	0 (0)
	Cancer (previous)	0 (0)	1 (2)
	Benign prostatic hyperplasia	5 (10)	2 (4)
	Prostate Cancer	0 (0)	0 (0)
	Chronic renal disease	0 (0)	0 (0)
	Liver fibrosis/cirrhosis	0 (0)	0 (0)
	Clinical depression	5 (10)	0 (0)
	Anxiety	7 (15)	5 (10)
ADHD	6 (13)	4 (8)	
Insomnia	5 (10)	2 (4)	

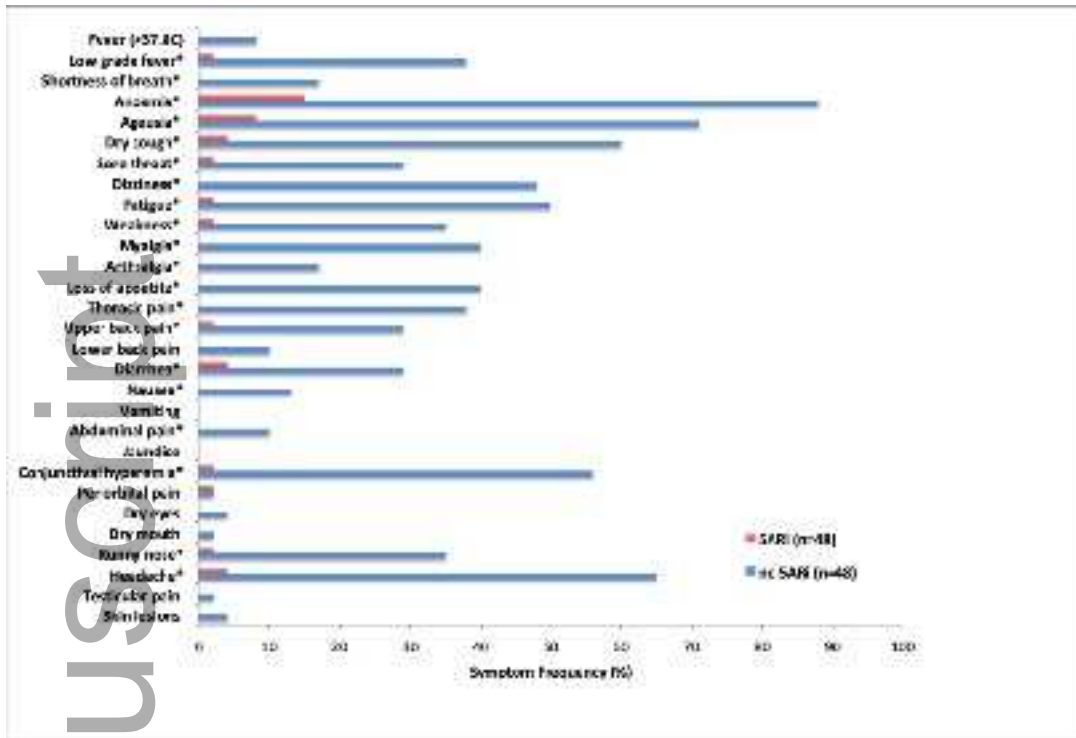
	Hypogonadism	3 (6)	4 (8)
	Hypothyroidism	2 (4)	1 (2)
	Autoimmune	0 (0)	0 (0)
	Other Diseases	0 (0)	0 (0)
<hr/>			
MEDICATIONS Used, No. (%)			
<hr/>			
ANTI-HYPERTENSIVES	Beta-blocker	4 (8)	3 (6)
	ECAi	5 (10)	4 (8)
	Angiotensin II receptor blockers	9 (19)	9 (19)
	Loop diuretics	1 (2)	0 (0)
	Thiazide diuretics	4 (8)	4 (8)
	Calcium channel blockers	6 (13)	4 (8)
	K-sparing diuretics	0 (0)	1 (2)
LIPID REDUCING AGENTS	Statins	23 (48)	14 (29)
	Others	2 (4)	2 (4)
ANTI-COAGULANTS	Aspirin	2 (4)	2 (4)
	Clopidogrel	0 (0)	0 (0)
	Xa factor inhibitors	3 (6)	0 (0)
ANTI-DIABETICS	Metformin	11 (23)	10 (21)
	GLP1R analogue	3 (6)	2 (4)
	SGLT2 inhibitors	5 (10)	2 (4)
	DPP4 inhibitors	4 (8)	3 (6)
	Sulfonylureas	1 (2)	0 (0)
	Glitazone	0 (0)	1 (2)
	Acarbose	0 (0)	0 (0)
	Insulin	0 (0)	1 (2)
	Orlistat	2 (4)	5 (10)
HYPOTHYROIDISM	Levothyroxine	2 (4)	1 (2)
	Liothyronine	0 (0)	0 (0)
HYPOGONADISM	Testosterone	1 (2)	4 (8)
	Aromatase inhib. or SERMs	0 (0)	0 (0)
CENTRAL-ACTING DRUGS	Sedative	7 (15)	1 (2)
	SSRi	9 (19)	2 (4)
	Other antidepressants	2 (4)	3 (6)
	Benzodiazepines	2 (4)	0 (0)
	Atypical antipsychotics	0 (0)	0 (0)

	CNS stimulants	8 (17)	3 (6)
ANDROGENETIC ALOPECIA (others)	Finasteride	0 (0)	0 (0)
	Oral minoxidil	1 (2)	0 (0)
BPH (others)	Alpha-1 adren. blockers	3 (6)	2 (4)
ANDROGEN DEPRAVATION	GnRH analogues and inh., NSAA, others	0 (0)	0 (0)
ERECTILE DYSFUNCTION	Sildenafil, tadalafil, others	8 (17)	5 (10)
SUPPLEMENTATION	Omega-3	3 (6)	2 (4)
	Vitamin D	9 (19)	5 (10)
	Zinc	1 (2)	1 (2)
	Biotin	5 (10)	2 (4)
	Vitamin C	2 (4)	3 (6)
VACCINES	BCG	48 (100)	48 (100)
	Influenza (in 2020)	7 (15)	7 (15)
	Pneumococcal (in 2020)	6 (13)	7 (15)
LIFESTYLE	Current Smoker (>2pk/week)	2 (4)	1 (2)
	Physical activity (>150 min/week)	22 (46)	11 (23)

**Table I. Baseline Characteristics of Androgenetic Alopecia Men with COVID-19 by Use and Nonuse of 5-alpha-reductase Inhibitors.**

Shown are SARS-CoV-2 men with androgenetic alopecia using 5-alpha-reductase inhibitors (5ARi) compared to propensity score matched androgenetic alopecia men not using 5-alpha-reductase inhibitors (no 5ARi).





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