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Does Angiotensin II receptor blockers increase the risk of SARS-CoV-2 infection? A real-life experience

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Abstract. – OBJECTIVE: Since the start of the COVID-19 pandemic, millions of people have been infected with thousands of deaths. Few data regarding factors that increase the risk of infection are available. Our study aimed to evaluate all people living in retirement homes (PLRNH) and identify factors that could increase infection risk in a close community.

MATERIALS AND METHODS: We conducted a retrospective study enrolling all PLRNH, where at least one SARS-CoV-2 infected person was present. Variables were compared with Student's t-test or Pearson chi-square test as appropriate. Uni- and multivariate analyses were conducted to evaluate variables' influence on the infection.

RESULTS: We included 452 PLRNH; 144 (31.7%) were male, with a mean age of 82.2±8.6 years. People with a positive swab for SARS-CoV-2 were 306 (67.4%). A significant difference between SARS-CoV-2 infected and not infected was observed in the percentage of those receiving chronic treatment with Angiotensin II receptor blockers (ARBs) (18.6% *vs.* 9.5%, *p*=0.012). On the contrary, there was no difference in the proportion of those receiving ACE inhibitors (ACE-I) (21.2% *vs.* 23.6%, *p*=0.562). At multivariate analysis, people with mental illness and cancer had an increased risk of being infected. Furthermore, receiving ARBs as a chronic treatment was an independent predictor of infection risk [OR 1.95 (95% CI 1.03-3.72) *p*=0.041].

CONCLUSIONS: Our data suggest that, in close communities, such as retirement nursing homes, the receipt of ARBs increased the risk of acquiring SARS-CoV-2 infection. However, before changing an important chronic treatment in a fragile population, such as the elderly living in retirement nursing homes, clinicians should carefully evaluate the risk-benefit ratio.

Key Words:
COVID-19, SARS-CoV-2, Angiotensin II receptor blockers.

Introduction

Since December 2019, when the first case of SARS-CoV-2 infection was described, Coronavirus disease 2019 (COVID-19) caused thousands of deaths worldwide. COVID-19 represents a real threat to global health and economics and should be managed with innovative approaches[1,2]. SARS-CoV-2 infects the lung alveolar epithelial cells, primarily causing pneumonia and Acute Respiratory Distress Syndrome (ARDS)[3,4]. Common COVID-19 symptoms include fever, cough, and dyspnea, while fatigue, headache, anosmia, ageusia, cutaneous manifestation, and gastrointestinal symptoms are less common[5-11]. Several variables seem to be associated with worse outcomes, such as age > 65, pre-existing concurrent cardiological, and cerebrovascular disease[12]. Few data regarding factors that increase the risk of infection are available. Our study aimed to evaluate all people living in retirement homes (PLRNH) and identify factors that could increase infection risk in closed communities.

Materials and Methods

Study Conduction

We conducted a retrospective study, collecting medical records of PLRNH, where at least one SARS-CoV-2 infected person was present. Our

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team evaluated all people present in the facilities from April 9, 2020, to November 10, 2020.

The diagnosis was based on real-time PCR on nasopharyngeal swabs. Medical history and clinical data were collected; we extracted the demographic data, medical history, clinical symptoms, and clinical outcome.

Patient compliance was defined as the patients' possibility to adhere to medical advice on oral and intravenous treatment regimens, respiratory exercise, and medical devices. Autonomy was defined as the ability to perform any daily activity without assistance.

This research has to be part of the protocol "COVID-19-SS", approved by the Local Ethical Committee, with the protocol number PG/2020/9411.

Statistical Analysis

Data were elaborated as numbers on total (percentages), means ± standard deviation, as appropriate after evaluating the normality of distribution with the Kolmogorov-Smirnov test.

Continuous variables with parametric distribution were compared with Student's *t*-test. Categorical variables were evaluated with the Pearson chi-squared test.

Univariate analysis was conducted to evaluate variables' influence on the infection. Independent variables resulting in a $p<0.2$ at univariate analysis were included in the model. The significance level was defined as $p<0.05$.

Results

Overall, 452 PLRNH were included; 144 (31.7%) were male, with a mean age of 82.2±8.6 years (Table I). The most common comorbidity was hypertension, present in 293 (64.5%) people, followed by neurological syndromes and psychiatric disorders with 226 (49.8%) and 186 (41%) cases, respectively. People with a positive swab for SARS-CoV-2 were 306 (67.4%). A significant difference between SARS-CoV-2 infected and not infected PLRNH was observed in the percentage of those receiving chronic treatment with Angiotensin II receptor blockers (ARBs) (18.6 *vs.* 9.5%, $p= 0.012$). On the contrary, there was no difference in the proportion of those receiving ACE inhibitors (ACE-I) (21.2% *vs.* 23.6%, $p=0.562$). Dividing the cohort in those receiving treatment with ARBs and those who were not, the only significant difference was the presence of hypertension, diabetes, and cardiovascular disease (CHD). No difference has been seen regarding mortality in people treated with ARBs compared with those who were not (Table 1).

At the multivariate analysis (Table II), people with mental illness [Odds Ratio (OR) 1.1 (95% Confidence Interval (CI) 1.09-2.58) $p=0.018$], and cancer [OR 3.2 (95%CI 1.2-8.57) $p=0.02$] had an increased risk of being infected. Besides, receiving ARBs as a chronic treatment significantly increased the infection risk [OR 1.95 (95%CI 1.03-3.72) $p=0.041$].

Table I. Characteristics of 454 people living in retirement nursing homes divided into people who have ARBs in the chronic treatment and people who have not.

	Overall (454)	ARBs (71)	No ARBs (383)	*p*-value
Age (years), mean ± SD	82.2±8.6	84.9 ± 8.6	81.7 ± 11	0.018
Gender, n° (%)				
Male	144 (31.7)	20 (28.2)	124 (32.4)	
Female	310 (68.3)	51 (71.8)	259 (67.6)	0.484
BMI > 30, n° (%)	79 (17.4)	17 (23.9)	62 (16.2)	0.116
Hypertension, n° (%)	293 (64.5)	71 (100)	222 (58)	< 0.001
Diabetes mellitus, n° (%)	91 (20)	22 (30.1)	69 (18)	0.012
COPD, n° (%)	87 (19.2)	17 (23.9)	70 (18.3)	0.265
CHD, n° (%)	183 (40.3)	43 (60.6)	140 (36.6)	< 0.001
Mental disorders, n° (%)	186 (41)	31 (43.7)	155 (40.5)	0.627
Neurological disorders, n° (%)	226 (49.8)	30 (42.3)	196 (51.2)	0.161
Kidney failure, n° (%)	33 (7.3)	5 (7.1)	28 (7.3)	0.936
Malignancy, n° (%)	36 (7.9)	3 (4.2)	33 (8.6)	0.209
Hypokinetic disease, n° (%)	120 (26.4)	20 (28.2)	100 (26.1)	0.727
Autonomy, n° (%)	156 (34.4)	28 (39.4)	128 (33.4)	0.327
SARS-CoV-2 TNF positive, n° (%)	306 (67.4)	57 (80.3)	249 (65)	0.012
Symptoms COVID-19, n° (%)	180 (39.6)	41 (57.7)	139 (36.3)	0.001
Deaths due to SARS-CoV-2, n° (%)	77 (17)	13 (18.3)	64 (16.7)	0.741

ARBs: Angiotensin II receptor blockers; SD: standard deviation; BMI: body mass index; COPD: COPD: chronic obstructive pulmonary disease; CHD: cardiovascular disease; COVID-19: Coronavirus Disease 19.

Table II. Univariate and multivariate logistic regression estimates of factors associated with SARS-CoV-2 infection.

	Unadjusted		Adjustedl	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Gender				
Female *vs* Male	1.2 (0.78-1.84)	0.397		
Comorbidities				
BMI > 30	1.42 (0.82-2.44)	0.206		
Hypertension	1.21 (0.81-1.82)	0.345		
Diabetes	1.66 (0.98-2.82)	0.057	1.41 (0.82-2.44)	0.218
COPD	1.34 (0.79-2.25)	0.268		
CHD	1.51 (1.01-2.27)	0.049	1.43 (0.92-2.2)	0.108
Mental illness	1.8 (1.19-272)	0.005	1.1 (1.09-2.58)	0.018
Neurological	0.72 (0.48-1.07)	0.102	0.68 (0.45-1.04)	0.075
Kidney failure	096 (0.45-2.05)	0.926		
Cancer	3.22 (1.23 –8.47)	0.018	3.2 (1.2-8.57)	0.02
Compliance	1.29 (0.86-1.92)	0.222		
Hypokinetic disease	1.75 (1.08-2.80)	0.021	1.62 (0.98-2.69)	0.059
Chronic Treatment				
ARBs	2.19 (1.18-4.08)	0.013	1.95 (1.03-3.72)	0.041
ACE inhibitor	0.87 (0.55-1.39)	0.562		

CI: confidence interval; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CHD: cardiovascular disease; ARBs: Angiotensin II receptor blockers; ACE: angiotensin-converting enzyme.

Discussion

To our knowledge, this is the first study that evaluated the role of the receipt of ARBs on SARS-CoV-2 infection risk in close communities, such as retirement nursing homes, where the transmission rates of SARS-CoV-2 is exceptionally high. Regarding antihypertensive drugs, the interaction between SARS viruses and ACE 2 has been proposed as a potential risk factor of infectivity. For this reason, some concerns have been raised about their use, for a possible transmission increase, related to increased host susceptibility[13]. Interestingly, our findings diverge from most common literature findings since ACE-I did not increase the risk, as described by most of the literature on SARS-CoV-2 infection and outcomes[13-16]. On the contrary, our data seem to support the hypothesis that chronic treatment with ARBs can raise the possibility of contracting SARS-CoV-2 infection.

Mancia et al[17] conducted a case-controlled study finding that ARBs and ACE-I were both more frequently prescribed in SARS-CoV-2 infected patients than in not infected, but neither ARBs nor ACE-I, in the multivariate analysis, had a significant association with the risk of SARS-CoV-2 infection.

Our study did not find significant differences in symptoms' appearance and mortality in people who received ARBs. The role of ARBs in the severity of the disease is debated in the literature. Zhang et al[18] reported that mortality risk was lower in inpatient that had ACE-I, or ARBs, as a chronic treatment, than ACE-I/ARB nonusers. Reynolds et al[19] found no differences regarding the severity of COVID-19 among patients treated with five common classes of antihypertensive medications.

Conclusions

Shortly, our data suggest that ARBs resulted in having a role in the SARS-CoV-2 infection in closed communities. However, before changing an important chronic treatment in a fragile population, such as the elderly living in retirement nursing homes, clinicians should carefully evaluate the risk-benefit ratio.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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