



## CASE REPORT

# Ivermectin and COVID-19 in Care Home: Case Report

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## Introduction

COVID-19 appeared at the end of December 2019 in China in the city of Wuhan before spreading around the world in just a few months. At the end of May 2020, among 77 000 people living in care home in Paris area, 16 940 (22 %) were estimated positive to Covid19 and 5 600 (33 % among positive ones) had a Covid19 related death [1,2]. When lockdown started on March 15, 2020, old age and comorbidity features including heart failure, diabetes, respiratory failure, obesity, were known to be a high-risk of severe Covid19 infection, so care homes were considered as vulnerable. Starting on March 15, 2020, strict isolation measures were applied in our Scarron nursing home, including mandatory mask-wearing for all staff involved and a ban on visits. Nonetheless, in March, we still lacked protective equipment, forcing caregivers to wear their masks for more than four hours straight. In addition, gowns were only available in small quantities.

On April 3, 2020, a cluster was observed in the nursing home including 68 residents in total, and all residents and staff were tested. We took a series of measures intended to limit contagion in the nursing home: creating two separate areas, introducing stricter confinement to rooms for all residents, tightening rules for staff and optimizing the course of treatment for sick staff.

In this period, many centers and groups employed a multitude of novel therapeutic agents empirically and within clinical trials [3,4]. Asking for treatments possibilities, the infected patients were clearly informed over the broad debate concerning many drugs, of which hy-

droxychloroquine and azithromycin. Ivermectin (IVM) was suggested empirically as known for in vivo anti dengue Flavivirus [5] and *in vitro* antiviral activity against HIV [6] dengue [7,8] and chikungunya [8]. In care home IVM is an option for treatment of scabies, including for community infection control [9]. In the other hand IVM is worldwide used for the treatment of river blindness caused by onchocerciasis infection [10]. Side effects including mainly allergic rash and decrease in tension, were declared at a very low rate [9,10].

## Patients and Methods

All residents and staff were tested: 10 of 32 (31.2%) of the staff and 25 of 68 (36.8%) of residents (23 from the outset and 2 within the following weeks) had a positive PCR result.

Collegial staff suggested treatment by IVM at usual anti helminthic doses. Known side effects are mainly dermatologic rash with itching and hypotension, vomiting, diarrhea, in people treated for onchocercia. In scabies treatment, sides effect rate appeared very low [9]. Detailed information was given to the patients accompanied by their family and in contact with their own general practitioner. Consent from informed patients was obtained from each patient.

Of the 25 PCR-positive patients, 10 chose to take the IVM treatment (group 1) and 15 chose not to take IVM (group 2). Patients of the group 1 received a single dose of 200 micrograms/kg body weight. Individual daily medical check was scheduled for the 2 months of the lockdown period that lasted from April 3 to May 15, 2020 for all patients. The monitoring protocol, imple-



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mented with the nurses, included heart rate, blood pressure, temperature and oxygen saturation measurements in the morning and evening for all residents. Lethal, high symptomatic, few symptomatic, and asymptomatic Covid19 disease were registered from April, 3, to May, 15 2020.

Statistical analysis used Fischer test for small groups.

## Results

Among the 68 residents, there were 51 females and 17 males. Among the 25 Covid19 positive residents, there were 13 females and 12 males, showing a statistical difference in the sex repartition in Covid19 positive residents and the whole resident community ( $p = 0.0014$ ). Sex ratio was similar in both Covid19 positive groups (Female were 4/10 in group 1 and 9/15 in group 2,  $p = 0.42$ ). The mean age was 83.5 years in group 1 and 81.8 years in group 2 ( $p = 0.9$ ). Overall and Covid19 specific comorbidities were present in all patients with an average of 3 (Table 1).

The concomitant treatments were as per the consensus at the time [11]: prophylactic anticoagulation included enoxaparin  $n = 4$ ; tinzaparin  $n = 2$ ; rivaroxaban  $n = 5$ ; apixaban  $n = 1$  patient; acenocoumarol  $n = 1$  (2) antibiotics for lung involvement included ceftriaxone  $n = 6$  patients; amoxicillin/clavulanic acid  $n = 4$ ; doxycycline  $n = 4$ ; ciprofloxacin  $n = 2$  (3) oxygen at 6 liters /minute, average Flow was added in 13 patients, for about 8 days.

**Table 1:** Reported comorbidities.

Comorbidities	Group 1	Group 2
<b>Increased risk of severe Covid19 infection</b>		
Hypertension	5	8
Chronic Bronchitis	4	5
Obesity	2	1
Atrial Fibrillation	2	2
Diabetes	0	2
<b>Overall comorbidities</b>		
Depression	3	3
Psychosis	1	3
Parkinson	1	1
Dementia	5	7
Epilepsy	2	1

**Table 2:** Severity of infections among the two groups of patients.

Period from 3 April 2020 to May 15 <sup>th</sup> 2020 Covid19 infected patients	Group 1 IVM	Group 2 no IVM	p
Death	1	5	0.3
Highly symptomatic	2	5	
Few symptomatic	4	2	
No symptomatic	3	3	
Total	10	15	0.5

Mortality occurred in 1 patient in the group 1 and 5 of the group 2 ( $p = 0.34$ ). Two other of the 43 PCR negative residents, died during the same period. So the mortality rate for the 2 months period was 6/25 (24.0%) in PCR positive residents and in 2/43 (4.6%) in PCR negative residents showing statistical difference ( $p = 0.004$ ). Moreover for the last three years before Covid19 pandemic, the mortality rate in this care home was 19 deaths/year for 68 residents, i.e. 3.17 for 2 months (4.6%) that appeared similar to the rate of mortality in PCR negative residents, suggesting an over mortality rate related to Covid19 PCR positivity. Four of the 6 dead patients were male showing a statistical difference in sex repartition ( $p < 0.01$ ).

Highly symptomatic with lung involvement with desaturation requiring oxygen therapy, prolonged diarrhea, severe impairment of general health occurred in 2 patients of group 1, and 5 in the group 2 ( $p = 0.65$ ). Few symptoms including fever for a few days, disorientation, urinary tract infection, slight impairment of general health, occurred in 4 patients in group 1 and 2 in group 2 ( $p = 0.17$ ). Asymptomatic occurred in 3 patients in group 1 and 3 patients in group 2 ( $p = 0.65$ ) (Table 2).

The side effects included 1 allergic rash, recovered within 48 hours, related to IVM. Orthostatic hypotension: one case was related to polypharmacy including amlodipine, levodopa, and mianserine.

PCR test repeated on day 22, from positivity date, were negative for all patients, PCR test repeated on day 43 were negative for every patients.

## Discussion

Covid19 pandemic could reach a mortality rate of 30 % in community of elderly people exhibiting at least 3 risk factors of severe infection [1]. Since 1989, IVM is an anthelmintic used for onchocerciasis and currently used every 12 months to protect populations from onchocerciasis in areas at high risk of contamination [10]. In France IVM is used for treatment of scabies, including for community infection control using a single dose of 200 micrograms/kg, repeated once, if necessary, 15 days later [12]. In the same period than our current reports, C. Bernigaud, et al. reported severity and mortality cases for Covid19 infection, lower in care home residents treated for community Scabies. Residents and staff were treated for a community Scabies using IVM 200 micrograms/kg at D0 and D7 at the beginning of

March 2020. In that care home 69 residents with a median age of 90 years, 78,3% of female, and 98.6% exhibiting at least 1 comorbidity risk factor of covid19 severe infection, were so treated with IVM. The rate of Covid19 infection were 1.4% in that care home compared to 22.6% in 45 home cares including 3062 resident people of the same French department of Seine et Marne near Paris. All the cases of the department were declared to French Health authorities ARS. Mortality related to Covid19 infection showed a rate of 4.9% of 3062 resident people versus 0% of 69 residents previously treated with IVM for community scabies [12].

In the other hand a study of prevalence study of COVID 19 in the different countries of Africa, has suggested a lower frequency of COVID 19 and lower mortality (-28%) in areas where people have been treated for onchocerciasis, with IVM [13]. A prospective trial called SAINT has been started with as primary objective to determine the efficacy of a single dose of IVM administered to low risk non severe covid-19 patients in the first 48 h after symptoms onset to try to reduce the proportion of patients with detectable SARS-CoV-2 RNA by PCR test from nasopharyngeal swab at day 7 post-treatment. Patients over 60 and with co-morbidities are excluded. This trial is going on [14].

*In vitro* Caly L, et al. [15] suggested effect of IVM on COVID 19 virus in Australia, showing a division by about 4000 in 48 hours in the amount of virus in a culture to which IVM is added. The pathophysiological hypothesis accepted is based on inhibition of virus transport across the nuclear membrane by preventing binding to the importin alpha-1/beta-1 protein [15,16].

IVM targets the host nuclear transport importin  $\alpha$ / $\beta$ 1 heterodimer which the virus relies for the replication and assembly of new virions [16]. This drug was shown to inhibit SARSCoV-2 *in vitro* replication for up to 48 h at a concentration of 5  $\mu$ M [3].

The 50 % inhibition concentration (IC50) was determined as 2  $\mu$ M which was much higher than the maximum plasma concentration [15]. A study was performed aiming to predict total (bound and unbound) and unbound plasma concentration-time profiles after the administration of FDA approved dose (200 mg/kg), 60 mg/kg and 120 mg/kg. The results of this study showed that plasma concentrations did not reach the IC50 even at doses higher than the approved [3]. However studies with animal models have shown up to 3-fold higher levels in pulmonary tissue than in plasma one week after oral dosing [17]. Moreover the lipophilic nature of the drug, with strong protein binding, may be favorable in the elderly population, increasing distribution and accumulation because the proportion of lipids in the body is higher (delayed effect possible) and because of the increased free component (because of the often low protein concentration in the elderly).

The anti-inflammatory effect of IVM has been suggested in acne rosacea, and in allergic asthma [18]. Recently JP Changeux had described the nicotinic acetylcholine receptor, as typical allosteric machine. Pharmacological effectors, referred to as allosteric modulators, are  $Ca^{2+}$  ions and IVM [19].

Giving the epidemiological data showing current smoking status appeared to be a protective factor against the infection by SARS-CoV-2, the nicotinic acetylcholine receptor has been suggested to play a key role in the pathophysiology of Covid-19 infection and might represent a target for the prevention and control of Covid-19 infection [20].

Our current study shows limits of no blind treatments, and a small cohort of patients. Prospective controlled studies are needed and the SAINT trial results are expected.

Given that this is not a double-blind study and the sample size is small, it is not possible to reach a conclusion about the efficacy of ivermectin in treating COVID-19 in a geriatric clinical setting; further randomized studies are needed.

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