COVID-19 SARS-CoV-2 Zoonotic Risk from Domestic and Exotic Animals and Possible Mitigation by Mesenchymal Stem Cell Therapy

Robert J. Harman, DVM, MPVM[1]

Michael Haverkate, DVM[1]

Christopher J. Rogers, MD[2]

[1]VetStem Biopharma, Inc., Poway, CA

[2]Personalized Stem Cells, Inc, Poway, CA

Correspondence : bharman@vetstem.com

KEY WORDS: COVID-19, Stem Cell, test, Therapy

INTRODUCTION

In late December 2019, multiple cases of severe respiratory distress with an unknown cause were reported in Wuhan, in the Hubei province of China. In January, a highly contagious novel coronavirus (SARS-CoV-2) was identified as the cause, resulting in a global pandemic. As of April 4, 2020, the World Health Organization had reported over 1,200,000 confirmed cases and more than 64,000 deaths in more than 180 countries and 200 territories.

Beginning in March 2020, confirmed reports of COVID-19 antigen test positive dogs, cats, ferrets and captive exotic animals began to emerge in the news. With an estimated 135 million domestic cats and dogs in the United States alone, their susceptibility to SARS-CoV-2 raises critical questions regarding the impact our pets will have on the ongoing COVID-19 pandemic.

There are several key questions regarding domestic and captive exotic animals relative to COVID-19: (1) can they contract COVID-19; (2) what is the severity; (2) can they transmit SARS-CoV-2 virus within or between domestic/exotic animal species, and (3) can they transmit SARS-CoV-2 to humans.

ANIMAL CASES OF COVID-19

To date, there have been seven confirmed cases of COVID-19 in non-human species: two dogs in China, one domestic cat in Belgium, one domestic cat in China, one Malayan tiger at the Bronx zoo in New York, and on 4/22/20 two domestic cats in New York. These cases were confirmed using antigen testing[†*]. Animals that have had close contact with these confirmed positive cases were also quarantined. Of the 2 confirmed canine cases, one 17-year-old dog, that exhibited no respiratory signs, died

** https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=33684*

† https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=33455

from unknown causes after being released from quarantine and another dog exhibited no clinical signs. One domestic cat was being treated for moderate respiratory and gastrointestinal signs, but the other domestic cat didn't exhibit symptoms. The Bronx Zoo tiger exhibited only mild respiratory signs. There were also several lions at the Bronx Zoo that exhibited respiratory disease, but none were tested for COVID-19 antigen•‡.

The report of the two domestic cats in New York is the in domestic pets in the US and were reported by the CDC and the USDA§. These cases lived in two different households in New York. The first cat tested positive after showing mild respiratory signs and there are no known positive people in this home. The second cat testing positive also showed mild respiratory signs and there was a COVID-19 positive test person in the home prior to the cats' illness. The COVID-19 positive tests in the cats were confirmed at the National Veterinary Services Laboratory.

These seven positive cases are not suggestive of severe clinical disease as has been associated with SARS-CoV-2 infection in humans. In an experiment performed at the Harbin Veterinary Research Institute in China (HVRI), five cats (eight months old) were intranasally inoculated with high levels of SARS-CoV-2 [1]. There were viral RNA and infectious viral particles present after three days, but none of them were documented to have developed clinical symptoms of disease. There is no experimental or naturally occurring evidence, to date, to support that animals infected with SARS-CoV-2 develop severe clinical disease [1].

Zhang et al. has recently reported on a serologic survey of domestic cats in Wuhan, China [2]. A total of 102 cats in animal shelters or pet hospitals in Wuhan were samples between January and March 2020. A negative cohort of 39 cat serum samples from March and May 2019 were tested with no positive results. Antibodies were assayed using ELISA and viral neutralizing tests. A total of 14.7% were positive for ELISA and 10.8% further positive for viral neutralizing tests. There was no cross-reactivity with type I or II feline infectious peritonitis virus. Tis data may indicated that these cats became infected during the Wuhan COVID-19 outbreak.

TRANSMISSION BETWEEN ANIMALS

The epidemiology of SARS-CoV-2 demonstrates human-to-human contact and transmission of virus laden respiratory droplets [3]. The experiment by the Harbin Veterinary Research Institute explored the susceptibility and transmissibility of SARS-CoV-2 in several species. Their data showed that certain species more readily amplify the virus than others, specifically that SARS-CoV-2 can replicate in the upper and lower airways of cats and upper airways of ferrets. The experiment suggests that the virus was passed via respiratory droplets between cats, resulting in one exposed cat out of the three becoming infected with the virus. The exact design of the cage set up was not described, so other modes of transmission are not ruled out. The summary of this research was published online but has not yet been peer reviewed [1]. It must be considered that the intranasal introduction of a high dose of pathogen does not represent the normal conditions of cat-cat or cat-human interaction. The Harbin researchers concluded "These results indicate that SARS-CoV-2 can replicate efficiently in cats, with younger cats being more permissive and, perhaps more importantly, the virus can transmit between cats via the airborne route" [1]. The data show that infection is possible but does not implicate cats as routes of transmission for SARS-CoV-2 to human. It is currently unknown whether animals can transmit the SARS-CoV-2 virus to animals of different species, but the Bronx Zoo report did indicate that the known tiger likely transmitted to the adjacent lions.

‡ https://www.aphis.usda.gov/aphis/newsroom/news/sa_by_date/sa-2020/ny-zoo-covid-19
§ https://www.cdc.gov/media/releases/2020/s0422-covid-19-cats-NYC.html

ANIMAL TO HUMAN TRANSMISSION OF COVID-19

Despite the fact that cats have been previously suggested as a mode of transmission in the SARS-CoV pandemic of 2003[**] , there is still no convincing evidence to support that SARS-CoV or SARS-CoV-2 is spread by felines to human [4]. Of the five confirmed cases of COVID-19 in domestic and captive exotic species, viral load was not reported, and the infective dose of viral particles is unknown. The HVRI experimental data does not demonstrate whether cats will develop enough of a viral load to transmit the virus to humans and does not suggest cats play a role in the transmission of the virus to humans. According to the World Organization for Animal Health (OIE), the United States Department of Agriculture (UDSA), and the Centers for Disease Control and Prevention (CDC), there is no evidence, to date, to support that domestic animals, livestock, or captive exotic animals can transmit SARS-CoV-2 to humans [††‡‡§§]. Given the rapid spread of the disease in the human population and the lack of research on SARS-CoV-2, animal and human health authorities are recommending enhanced personal hygiene and infection control measures for all individuals with close proximity to animals[***].

TRANSMISSION RISK REDUCTION USING STEM CELL THERAPY

Recommendations being made by the CDC and OIE remain cautious in the absence of information relating to the role animals will play in the COVID-19 pandemic. One method with published evidence for reducing risk of transmission from animals to humans or between animals is mesenchymal stem cell (MSC) therapy.

When administered by the intravenous route, MSCs will traverse directly to the lung capillary bed prior to any other organ capillary bed. As such, these cells can be easily delivered to the lungs. The following mechanisms related to the suppression of virus shedding suggest MSC therapy could reduce the risk of transmission between animals and other animals or humans.

MSCs suppress viral replication, viral shedding and virus-induced lung epithelial cell (LEC) damage [5]. Khatri et al demonstrated that MSC-derived extracellular vesicles (MSC-EVs), which are naturally secreted by MSCs, promote both anti-inflammatory and anti-viral properties via transfer of RNAs from EVs to LECs. Virus shedding measured in nasal swabs and virus titers in lung lysate were reduced by 100-fold in the MSC-EV treated group. Influenza virus induced LEC apoptosis and red blood cell hemagglutination were significantly reduced by MSC-EVs as well.

Influenza virus replication is further inhibited by MSC production of indoleamine 2,3-dioxygenase (IDO) [6] and LL37 by viral membrane degradation [7]. IDO has also been shown to suppress viral replication in hepatitis B, herpes simplex virus, cytomegalovirus and measles virus [8-11]. MSCs interact with immune cells and promote T-regulatory cells (Tregs) which improves influenza virus clearance [12, 13]. MSC-EV inhibition of viral replication has also been demonstrated in hepatitis C virus infected fibroblasts [14]. Rogers et al. just published a review of the evidence of MSC therapeutic value indicating that intravenous MSC therapy can reduce mortality and morbidity in humans and animals [15].

RECOMMENDATIONS

*** https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=33684*

†† *https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html*

‡‡ *https://www.usda.gov/coronavirus*

§§ *https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/*

*** *https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html*

To reduce the zoonotic risk to humans, animals with known COVID-19 or high-risk exposure can be administered intravenous mesenchymal stem cells. The scientific evidence indicates this can reduce viral shedding and therefore exposure level of other animals and humans. CDC, USDA, and AVMA recommendations, as described above, should also be followed to reduce zoonotic risks. Sources of stem cells and dose level recommendations will be presented in an additional manuscript by these authors.

SUMMARY

It is clear that animals can become infected with SARS-CoV-2 as the virus can be found in nasopharyngeal swabs in naturally and experimentally infected animals. These animals were both symptomatic and asymptomatic. It seems clear that the described animals in this manuscript were infected from humans, but animal-animal transmission is also demonstrated. If it is found that these animals can transmit this virus to humans, mesenchymal stem cell therapy may be a tool to reduce both the disease severity in the infected animals and the shedding of the virus and therefore zoonotic risk to humans.

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