USING OF LAB ANIMALS AS A MODEL TO STUDY THE DRUG TOXICITY IN COVID-19 (A review Article)

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ABSTRACT

The pandemic of COVID-19 is caused by the discovered strain of coronavirus, a type of virus known to cause human respiratory infections. This new strain was unknown before December 2019, when an outbreak of unidentified pneumonia occurred in Wuhan (China).As they are considered a vector for infection, the numerous fatal infections with the coronavirus have drawn attention to animals. Abundant attempts have been done to find the most effective cure with less toxicity and harmful effect to the human body, Furthermore the treatment results sometimes in a fatal medical toxicity that killed many people.

INTRODUCTION

A history of going to visit the local Seafood Market was an unifying trait linking some of the first patients diagnosed with COVID-19 in Wuhan, China. This was also recorded as a wet market in the sale of different animals(1, 2). As a result, several experts suggested that the disease originated in humans from the initial animal-to-human spread of the novel virus. SARS-CoV-2 has been biologically detected and catalogued and is associated with other related identified coronaviruses circulating between bats (such as coronavirus SARS and coronavirus MERS)(3). Bats are therefore thought to be the most likely main reservoir of that kind of novel coronavirus. However, the first case of COVID-19 occurred in Wuhan in a patient who had no connection to the seafood industry[1]. Bats are also noted as a carrier on Chinese markets (4). SARS-CoV-2 can also potentially be transmitted directly from bats to humans.

Additionally pets or other animals pose a serious risk to humans , however to date, there is no substantial evidence to date based on the early data on the transmission of SARS-CoV-2 to other animals. (5) However, given the growing critical interest, there are major health organizations, including the US Centers for Disease , In view of the speculation that wildlife species could be linked to this pandemic, the World Health Organization would also need the expertise of wildlife forensic experts in this collaborative approach. Indeed, a lot of professionals also hope that this crisis will co-exist (6,7). There are a limited lot of instances of spread, including domestic cats, from individual people to farm animals. Other cases include tigers and lions in a zoo in New York and minks in farms in the Netherlands (8). Animals have been shown to be afflicted in laboratory settings (9). In comparison, the virus does not appear to be infected or spread by rats, pigs, chickens, and ducks(10).

The centers of control of animal disease advises pet owners to restrict the contact between their pets and people out of their houses. Face coverings are not recommended for pets, as they may be harmed by face covering of the pet and must not be disinfected with cleaning products not certified for animal use. (11). Pets and other animals should not be touched by people sick with COVID-19.

Models of Animal

Several animal models were used to analyze COVID-19 with susceptibility vary depending on the particular makeup of the species to ACE2 (cellular receptor) (10). Small animal models are commonly used to study emerging viruses, but they also need to be genetically engineered or the virus needs to be genetically modified. The following animal breeds and species were used as animal models for the studying the pathogenesis of coronavirus scenario (Guinea Pig, *Mustela puters* , *Canis lupus*, *Macaca mulatta*, *Callithrix jacchus* Green Monkey of Africa, and *Homo sapiens*) (12).

Mice genetically engineered

Several inbreed mouse strains are being used for SARS-COV modeling of BALB/c,33 C57BL/634 & '129SvEv' infection ,35 as well as factor deficient mice such as Cd1-/-, Rag1-/-and Stat1-/-.34-37 ACE2 designation as SARS-CoV38 recep-

tor host initiated a major global interest in the creation of murine models representative of human disease (11).

Lately, ferret ACE2 was shown to generate the crucial impurities needed for SARS-CoV-2 RBD tying. (13) Animals were prone to SARS-CoV-2 infectious disease with Hepatitis infection in the respiratory tract, but only decreased amounts of virus were identified in the lungs (14) Despite the contagious virus was not detected outside of the respiratory system, viral RNA was discovered in the bowel, saliva, urine or rectal tract.

Golden Hamster

Syrian Golden Hamsters have been used to model of hamsters. Infectious diseases and animals which have been genetically altered have been generated (15). Hamsters are vulnerable to infection with SARS-COV In the respiratory tract, with comparable viral replication, but no viral replication ، Medical symptoms of sickness, rather than behavior loss (16).

Non-Human Primates

Only 5 percent of all animal testing are accounts for Non-Human Primates studies. Clinical translation of NHP research, however, is much greater. As they are similar to human models, rather than other animal models (١٧)

Several species of NHP have been investigated for SARS-COV such as Cynomolgus also African diseases، Green Monkeys & Common Monkeys, Monkeys of Squirrels and Tamarins of Mustards (18,19). Initial reports in Cynomolgus have carried out Viruses and macaques have been obtained from lung and nasal samples.

Miscellaneous contaminated animals

1- Bats

SARS-CoV-2 is obviously its roots are shared Bat ancestor SARS-Like COVs & COVs, it remains elusive current SARS-COV-2 for 40-70 years before dangerous (20). In wild bats, they are looking for additional proof & have conducted viral studies by a non-native species of host bat (21).

2-**Wild Cats**

Wild Cats SARS-COV has been detected and SARS-CoV-2 may be contracted by their owners (22). Cats are susceptible to experimentally infection The live virus was found in the tissues of the oral cavity, tonsils, lung, pharynx, and thin palate. But it was not found in the intestine and stool, which indicates that the virus does not exist in the digestive system and intestine (23). A Viral RNA from the lungs was cleared by 6 dpi in Additional tissues. Cats had smaller viral concentration of URT while in lung tissue, prolonged viral RNA shedding. Concordant to in wildly infected individuals, there were various degrees of respiratory disease (24, 25).

Animals Wild-Caught Positive

Although many species of animals have been infected with IAV175 and SARS-COV, pathogen, so far only a few have been correlated to SARS-COV-2, and many are susceptible predicated on their phylogenetic. Mink studies in farmlands in the Netherlands demonstrate the strain carried the actively transported from the spread the virus to the mink. (26, 27).

The respiratory disease of contaminated minks With inflammation of the lungs & pneumonia in china. That means a better model could be mink than ferret (٢٨) . There is a need for interrogation of representative animal models to identify pathogenesis induces and impacts and elucidates processes that in human research, They are validated and translated They ought to have individually and collectively, to reproduce human disease characteristics; genetically with adeno-viruses modified rats(29).

New research will identify additional studies، To accomplish these, features and refine templates, and also integrate representative chronic disease models for the description and treatment of Increased infection susceptibility pathways and COVID-19 (30, 31). Other animal models can be helpful, while they present major models. Non-Human Primates are closer for people & may be used for research before treatment by humans. Wild pets such as bats Natural resistance is critical (32).

The most important in the treatment of COVID- 19 and their associated toxicity include: Inhibitors of Viral Entry**,** Hydroxychloroquine and Chloroquine

Chloroquine alters ACE2 receptor glycosylation, which lowers ACE2 affinity for the coronavirus spike protein, thus decreasing in vitro SARS-CoV-2 entry (32). Also, the Toll-like receptor (TLR) pathway is inhibited by chloroquine and hydroxychloroquine, and the TLR pathway is involved in pro-inflammatory cytokine signaling Chloroquine was prevent infection with SARS-CoV-1 & sequence & structure homologies between SARS-CoV-1 (33).

That chloroquine reduce the infectivity of SARS-CoV2(34). in vitro research, chloroquine inhibits the entry of SARS-CoV-2[21]. Mortality from ventricular dysrhythmias and hypokalemia is correlated with doses greater than 5 grams of chloroquine(35). Within 1-3 hours of an overdose, cardiovascular failure and deep hypotension can occur (35). Seizures and CNS depression are among the neurological symptoms (36). Oxidative stress, may result in hemolysis. The blockade of the K channel result in an interval prolonged of QTc (37).

APN01

The human recombinant ACE22 is APN01 (Apeiron Biologics). This protein was first developed for the treatment of SARS(38). It is capable of handling. by preventing the entry of virus & reducing pulmonary damage, stopping the virus from attached to ACE2 in a dose dependent manner (39).

The signals are lost. By preventing SARS COV-mediated by ACE2 -contact, and thus physiological ACE22 restoration APN01 signaling can minimize acute pulmonary injury (40). In general, the inadvertent activation of the immune system results from unintentional immunogenicity and Recombinant binding. Triggering proteins to other receptors on the cell surface cascades of transduction cellular signal targeted. Inadvertent immunogenicity The formation of antibodies that deposited can result in as immune complexes in tissues.

Leronlimab (140 PRO)

Leronlimab (CytoDyn) is a humanized IgG4 research study. A monoclonal antibody was found on T against CCR5 receptors of lymphocytes (41). The first characterization of chemokine receptor 5 (CCR5) was for its function in Human Immunodeficiency as a co-receptor Viral penetration into white blood cells of the virus (HIV) Leronlimab is being observed. Repurposed and examined for patients as a therapeutic choice with COVID-19 suffering from respiratory problems such as a consequence of

COVID-19 (42). There is no serious adverse reaction. Reported adverse events or adverse events so far. Rationale by analogy with accepted oncology therapeutics, Acute humanized antibody toxicity can involve acute toxicity by immunosuppression, which is predisposed to opportunistic diseases viral-induced neoplasia or neoplasia; and immunostimulation (43). The storm of fevers, myalgia, cytokine storm Similar to acute lung injury (44).

Viral Inhibitors of Replication

Coronavirus genomes are nucleotide sequences that are efficiently processed as mRNA by human cells. The virus must make copies of its Genome, make virions, use Gene viral polymerase, and synthesize all of the proteins require to produce the virion, such as the viral genome and the capsid, Spike Proteins (45).

Analogs of Nucleotides

The primary objective of nucleic acid analogs is to interrupt the production process. Viral proteins RNA, that also makes it very difficult for diseased viral proteins to become storage centers for viruses (46).

Favipiravir and Remdesivir

Remdesivir (Gilead) is a precursor drug. It has shown efficacy in the laboratory (47). In addition to inhibition of viral polymerase, the nuclear polymerase is inactivated mitochondria by nucleoside leading to reduced mitochondrial protein synthesis and dysfunction.The toxic effects of nucleoside analogs are acidity, lactate elevation (49). Bone marrow suppression is observed in approximately 5% of patients (50). Myopathy and pancreatitis (51, 52).

Protease Inhibitors

Therapeutic agents prevent invading pathogens from being competent by adhesion and inducing viruses proteases for new virons., The proteins of viruses are so identical that the viral drug must be successful against more than one virus in order to avoid its replication (53).

Ritonavir-Lopinavir

Ritonavir is a potent inhibitor of cytochrome CYP 3A4. (Lopinavir-ritonavir with ribavirin) is used as a preventive therapy in the treatment of critically ill patients by health care practitioners (54,55). Although high-dose toxicity is low, Harmful drug confrontations can occur if the drug metabolism is slow (56). Toxicity cause liver damage and elevated transaminase levels (57). Tendinopathy has been reported with short-term prophylaxis (58). Protease inhibitors also cause lipodystrophy, which is characterized by underlying obesity, back-cervical fat deposition (buffalo) and limb wasting (59).

Miscellaneous Stuff

Azithromycin

Azithromycin is an antimicrobial macrolide that used suppress microbial protein binds to the 50S subunit of bacterium ribosome. It is used to help stop aggravation of COPD and reactive airway disease. The whole second utilization could be used. That's the immune regulatory effect of azithromycin on immune cells. Decreases the release of respiratory syncytial virus (60,61).

ACE and Ibuprofen Antagonists

There is fear in the media that the enzyme that transforms angiotensin is (ACE) inhibitors can increase SARS COV susceptibility— Number 2. Inhibitors of ACE will increase the expression of ACE2. The RBD Receptor-Binding of A high affinity for ACE2 is observed in SARS-CoV-2. Nonetheless, ACE It has been shown that inhibitors minimize viral entry by competitive entry. Inhibition of ACE2-binding spike protein in vitro (62). Lastly, coronavirus-infected alveolar cells express fewer ACE2 on the surface of their cells compared to normal in cells (63,64).

Risks often associated with transfusion of plasma include acute lung damage associated with transfusion (TRALI), Circulatory Overload Associated with Transfusion (TACO), and anaphylactic/allergic responses. Other less common hazards Include infection spread, febrile non-hemolytic reactions to transfusions, RBC all immunization, and responses to hemolytic transfusion . Analysis in which plasma was used to SARS treat and no adverse effects were recorded beyond mild influenzas A (H1N1) Infusion reactions, such as fever or chills. There were no major adverse effects in patients with SARS-CoV-2 (65).

استخدام الحيوانات المختبرية كنماذج لدراسة سمية الادوية في علاج كوفيد-١٢ (مراجعة علمية)

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الخلاصة

مرض كوفيد -١٩ هو مرض معدي يسببه فايروس مكتشف حديثا يدعى فايروس كورونا، وهو نوع من الفايروسات التي تسبب اخماج تنفسية. قبل كانون الاول عام ٢٠١٩ ، عندما لم يحدد الوباء في ووهان الصين بعد ، لم تكن تلك السلالة الجديدة معروفة بعد. عندما حدد المسبب الرئيس للمرض في عدد من الاصابات الخمجية القاتلة المتسببة بفايروس كورونا جذبت الانظار نحو الحيوانات. من بين المحاولات لإيجاد العلاج المؤثر ضد فايروس كورونا والذي يكون اقل سمية وخطرا على جسم الانسان حيث انه لازالت الاخطاء الطبية القاتلة احد الاسباب التي اودت بحياة الكثير من البشر.

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