

Casirivimab/Imdevimab: Possible Candidate for COVID-19 Treatment in Pets: Traditional Review

Casirivimab/İmdevimab: Evcil Hayvanlarda COVID-19 Tedavisi İçin Olası Bir Aday: Geleneksel Derleme

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ABSTRACT The coronavirus disease-2019 (COVID-19), over the last 3 years has globally resulted in catastrophic widespread losses. Prevention and control of this disease has become a global priority for researchers and medical professionals due to high mortality rates, treatment costs and various losses (economic and fatalities). In recent times, the fact that cats and dogs living in households which are being affected by the disease has caused panic among pet owners and animal lovers. Studies have shown that cats, especially young cats, are the group of animals which are most affected. Therefore, the treatment of COVID-19 in animals is an important topic for veterinary medicine. Monoclonal antibodies have also been considered a possible treatment modality due to the use of various agents to treat COVID-19 and the lack of clear demonstration of their efficacy. Casirivimab/imdevimab (CAS/IMD) is a monoclonal antibody cocktail approved for treating COVID-19. There was a high expectation that CAS/IMD combination directly affects the angiotensin converting enzyme-2 receptors, which plays an important role in the pathogenesis of the virus. Experimental and clinical studies have shown that CAS/IMD combination positively affects the prognosis of patients suffering from COVID-19, speeds up the recovery process and increases survival. We suggest that CAS/IMD can be considered protective in COVID-19 positive dogs and cats. The aim of this article is to review the studies related to the beneficial effects of CAS/IMD and its possible effectiveness in animals with COVID-19 to promote their research in future studies.

ÖZET Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], son 3 yılda küresel olarak trajik yaygın kayıplara neden oldu. Bu hastalığın önlenmesi ve kontrolü; yüksek ölüm oranları, tedavi maliyetleri ve diğer çeşitli kayıplar (ekonomik ve ölümler) nedeniyle araştırmacılar ve medikal uzmanları için küresel bir öncelik hâline gelmiştir. Son zamanlarda hastalıktan etkilenen hanelerde yaşayan kedi ve köpeklerin olması, evcil hayvan sahipleri ve hayvanserverler arasında da paniğe neden oldu. Araştırmalar, kedilerin, özellikle genç kedilerin, en çok etkilenen hayvan grubu olduğunu göstermiştir. Bu nedenle hayvanlarda COVID-19 tedavisi veteriner hekimliği için önemli bir konudur. Monoklonal antikorlar, COVID-19'u tedavi etmek için çeşitli ajanların kullanılması ve etkinliklerinin net bir şekilde gösterilmemesi nedeniyle olası bir tedavi yöntemi olarak kabul edilmiştir. Casirivimab/imdevimab (CAS/IMD), COVID-19 tedavisi için onaylanmış bir monoklonal antikor kokteylidir. CAS/IMD kombinasyonunun, virüsün patogeneğinde önemli bir rol oynayan anjiyotensin dönüştürücü enzim-2 reseptörlerini doğrudan etkilediği yönünde yüksek bir beklenti vardı. Deneysel ve klinik çalışmalar, CAS/IMD kombinasyonunun, COVID-19'dan muzdarip hastaların prognozunu olumlu yönde etkilediğini, iyileşme sürecini hızlandırdığını ve sağkalım oranını artırdığını göstermiştir. Dolayısıyla CAS/IMD'nin COVID-19 pozitif köpek ve kedilerde koruyucu olarak kabul edilebileceğini öneriyoruz. Bu derlemenin amacı, CAS/IMD'nin faydalı etkileri ile ilgili çalışmaları ve gelecekteki araştırmaları teşvik etmek için COVID-19'lu hayvanlarda CAS/IMD'nin olası etkinliğinin gözden geçirilmesidir.

Keywords: Casirivimab; imdevimab; COVID-19; pet animals; monoclonal antibody

Anahtar Kelimeler: Casirivimab; imdevimab; COVID-19; pet hayvanlar; monoklonal antikor

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In March 2020, the World Health Organization declared an international public health emergency over an outbreak of atypical viral pneumonia first described in Wuhan, Hubei Province, China.^{1,2} The cause was a new strain of coronavirus called coronavirus 2 (SARS-CoV-2) for the severe acute respiratory syndrome. Since then, the coronavirus disease-2019 (COVID-19) has spread to every country in the world, affecting hundreds of millions of people, so it was imperative to develop a safe and effective drug to control the pandemic and its socio-economic reflexes.³ Although several groups of drugs and vaccines have been developed to combat this virus, none of them have been reported to be completely effective. Because of this limitation, trials for new drugs are in full swing. Researchers, who have recently talked about the use of monoclonal antibodies and consider them promising mainly because they have a direct impact on the pathogenesis of SARS-CoV-2.⁴ Studies were conducted in line with these considerations, and therefore the combination of casirivimab/imdevimab was found to reduce hospitalization rates, pulmonary viral loads and have positive impact on prognosis.⁵

COVID-19 has recently been reported to infect and cause clinical signs in companion animals.⁶⁻⁸ Since the mechanism of action of SARS-CoV-2 is similar in companion animals, casirivimab/

imdevimab can be considered as a potential drug for viral treatment.

COVID-19, PETS AND THE IMMUNE SYSTEM

Veterinarians are faced with various pathogens that cause serious diseases in animals and the number of diseases is increasing daily. Although various established treatments are applied, the response to the pathogen mainly depends on the animal's immune system, a unique mechanism that fights pathogens, including viruses. Although the activation of this mechanism is necessary for the virus to attack, its excessive activation can lead to adverse effects.⁹ In recent studies, it has been established that COVID-19, which has become a major concern in humans, can also be transmitted to animals (Figure 1).⁶ Therefore, a new disease has been added to animal pathogens. In this way, the protection of animals and public health during this pandemic has become a target. Although dogs have milder symptoms than humans and recover early from the disease, it can sometimes be serious. Symptoms such as coughing, vomiting, dyspnoea and diarrhoea of varying severity may cause and affect animal welfare.¹⁰ Undeniably high rates of deaths and hospitalizations around the world are associated with the cytokine storm. Hyperinflammation thereby worsens clinical and laboratory conditions, leading to multi-organ failure.¹¹

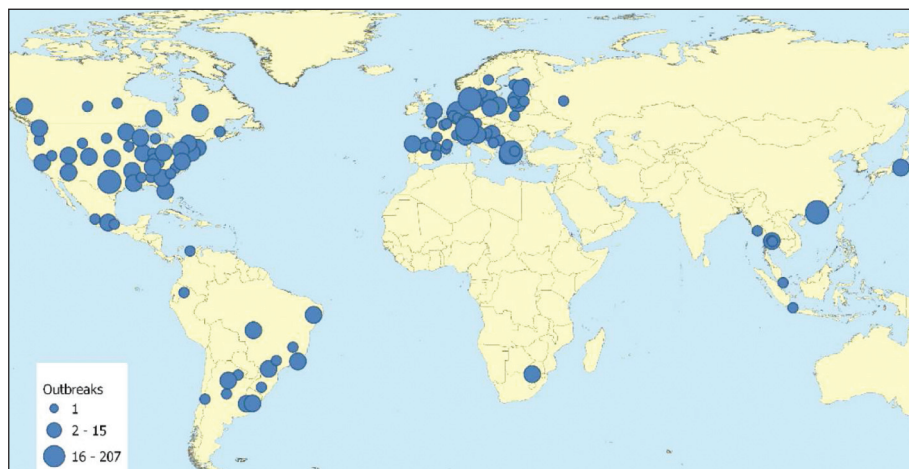


FIGURE 1: Global geographic distribution of SARS-CoV-2 outbreaks in animals reported to the World Organization for Animal Health (WOAH). Figure reproduced with permission from WOAH.²⁶

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

MONOCLONAL ANTIBODIES AND IMMUNE SYSTEM

Monoclonal antibodies (mAb) are proteins produced *in vitro* to help our immune system identify and destroy antigens which considered to be harmful.¹² These antigens can be proteins, bacteria, various viruses, or inflammatory cells. Therefore, mAbs have been used in modern medicine for treating various ailments such as cancers, various autoimmune diseases such as rheumatoid arthritis, osteoporosis, and infections such as respiratory syncytial virus in children and COVID-19.¹² Numerous vaccines against COVID-19 have been developed and used with considerable success. Although vaccines are thought to provide sufficient immunity against the virus, this may vary depending on the individual or situation. The successful launch of several candidate vaccines by the world's most sophisticated vaccine companies following phase 3 clinical trials has raised high hopes for controlling this pandemic. However, due to the lack of equitable access to vaccines, problems related to the global coverage of vaccine delivery has been especially seen in underdeveloped countries.¹³ In these cases, treatments to support the immune system such as mAbs are needed. Additionally, it is intended for use in patients who are not fully vaccinated or whose immunity wanes over time despite being fully vaccinated.¹⁴

CASIRIVIMAB/IMDEVIMAB AND COVID-19

The prevention of casualties due to COVID-19 in humans and animals has become one of the most important goals recently. Various treatment regimens including antiviral drugs, immunomodulators and antiparasitic drugs have been used to prevent the disease caused by SARS-CoV-2 and have been found to be effective against the virus to varying degrees.¹⁵ The new direction for researchers, who are constantly searching for a major drug group effective against COVID-19, is monoclonal antibodies.

The SARS-CoV-2 binds to angiotensin converting enzyme-2 (ACE2) and TMPRSS2 receptors in the host cell via the spike (S) proteins it contains and allows them to enter the host cell.¹⁶ Based on this information, research on the

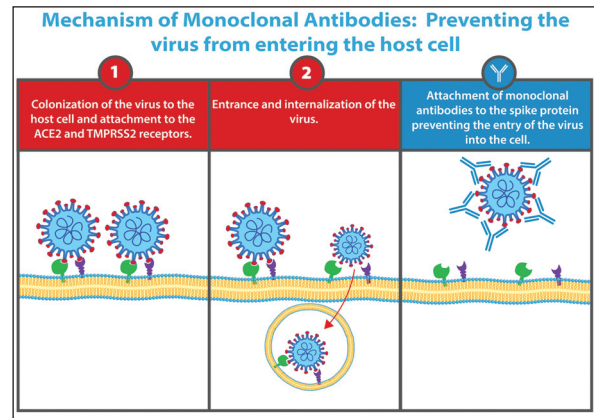


FIGURE 2: Monoclonal antibodies prevents the viral invasion by attacking and blocking the spike protein.^{5,15} ACE: Angiotensin converting enzyme.

development of a new drug or vaccine against COVID-19, it targets the S protein thus preventing the invasion of the virus.¹⁵ The monoclonal antibodies bind to the S proteins of the virus and avoid interaction with the ACE2 and TMPRSS2 receptors (Figure 2). In this way, the virus is excluded from the host cell preventing its access and ultimately stopping infections in the body.⁵ Because of this mechanism of action, mAbs are considered a possible preventative treatment option for COVID-19.

Casirivimab/imdevimab (CAS/IMD) is a monoclonal antibody cocktail approved for emergency use by the Food and Drug Administration and European Medicines Agency for treating COVID-19 in November 2020. These 2 neutralizing antibodies provide passive immunity against SARS-CoV-2 through inhibiting virus internalization (Figure 3).¹⁷ This cocktail has been the subject of attention in various studies.^{5,18}

The use of monoclonal antibodies for treating COVID-19 has been studied by Pallotta et al. and tests were carried out using 2 groups: a antibody treatment group and a placebo group.⁵ The CAS/IMD combination was chosen as the antibody treatment to be applied. The rate of hospitalizations and emergency room visits was found to be lower in the mAb treatment group (2.8%), compared to the placebo (6.5%). In a study by Hurt and Wheatley, the clinic investigated the effectiveness of a single 1,200 mg dose of CAS/IMD combination and the rate of hospitalized patients and deaths due to COVID19

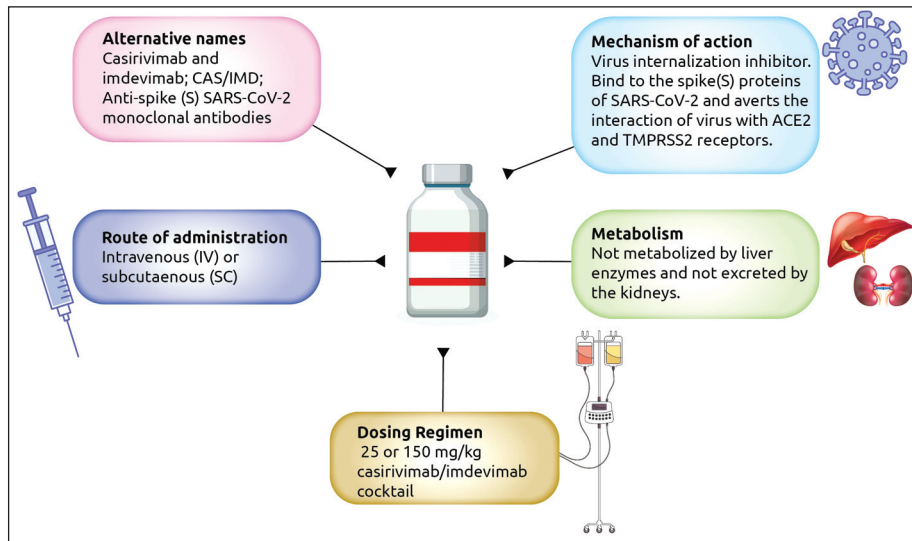


FIGURE 3: General features of CAS/IMD cocktail.^{5,20}

CAS/IMD: Casirivimab/imdevimab; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; ACE: Angiotensin converting enzyme.

was determined to be 1%, while this rate was 3.2% in the placebo group. Additionally, side effects were found to be 1.1% in the CAS/IMD combination and 4.0% in the placebo.¹⁵ In another study, 403 SARS-CoV-2 Delta peak positive patients eligible for monoclonal antibody therapy was considered. 112 patients on CAS/IMD treatment were observed with a hospitalization rate of 2.6% at 28 days, compared with 16.6% of the 291 high-risk patients who did not receive treatment.¹⁹ Many studies like these have been conducted and generally it has been claimed that the combined use of 2 monoclonal antibodies, CAS/IMD is effective in COVID-19 cases ranging from mild to severe.^{14,18} It has been at the forefront of studies because it reduces viral load and shedding and lowers the overall infection rate.²⁰

For treating COVID-19, CAS/IMD should be given in equal doses and as a single infusion over at least 60 min.²¹ Alternatively, it can be administered as a subsequent subcutaneous (s.c.) injection. For the efficacy of the applied treatment, the recommended dose for cats and dogs is 120 mg casirivimab plus 120 mg imdevimab, a total of 240 mg. To prevent viral mutations, it is recommended to use these 2 mAbs in a single combined dose and treatment should be started as soon as possible, within 10 days of the onset of symptoms.^{20,21} It is

considered an advantage that the effectiveness of CAS/IMD is not affected by patient characteristics such as age, gender, body weight, and conditions including albumin level and organ failures. Excretion and metabolization of monoclonal antibodies are neither carried out by the kidneys nor by the liver. Thus, drug interactions are unexpected, reducing the incidence of side effects.²⁰

Recently, CAS/IMD infusion was administered to 14 kidney transplant recipients who tested positive for SARS-CoV-2 by the Lui group.²² It was reported that they had no hypersensitivity reactions after the infusion and only one of the 14 recipients had a burning sensation in the hands, which was resolved by administering acetaminophen.²² This indicates; CAS/IMD treatment can be safely applied to SARS-CoV-2 positive kidney transplant recipients.

CAS/IMD AND PETS

mAb have been used in veterinary medicine for many years and are effective for treating many animal diseases. Canine lymphoma, an important and frequently found haematological cancer in dogs, is the largest example of the use of monoclonal antibodies.²³ Besides, another mAb used in veterinary medicine increases the possibility of treating atopic dermatitis and pruritus by binding to interleukin-31,

which plays a role in the pathogenesis of the disease.²⁴

The possibility of human-to-animal transmission of SARS-CoV-2 has led to attempts to find an effective treatment method in animals. Given the beneficial effects of mAbs, the CAS/IMD combination may be effective in cases of COVID-19 in animals and humans. In the rhesus macaque and hamster model study, CAS/IMD was reported to have prophylactic and therapeutic effects against SARS-CoV-2.²⁵ It significantly reduced viral load, pneumonia-related symptoms, and weight loss due to infections.²⁵

CONCLUSION

Considering the literature review, CAS/IMD combination could be a possible treatment method for COVID-19. Especially in macaques and hamsters that tested positive for COVID-19, beneficial effects on the clinical situation were observed after receiving treatment with monoclonal antibodies. However, the transmission of the SARS-CoV-2 from humans to dogs and cats led us to believe that CAS/IMD could also be effective in these animals.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Fatma Ender, Serkan Sayiner, Ahmet Özer Şehirli; **Control/Supervision:** Güzin Özkurt, Nurettin Abacıoğlu, Ahmet Özer Şehirli; **Data Collection and/or Processing:** Fatma Ender, Sevgi Gençosman, Deniz Ceylanlı; **Analysis and/or Interpretation:** Fatma Ender, Serkan Sayiner, Sevgi Gençosman, Deniz Ceylanlı, Güzin Özkurt, Nurettin Abacıoğlu, Ahmet Özer Şehirli; **Literature Review:** Fatma Ender, Serkan Sayiner, Sevgi Gençosman, Deniz Ceylanlı, Ahmet Özer Şehirli; **Writing the Article:** Fatma Ender, Serkan Sayiner, Nurettin Abacıoğlu, Ahmet Özer Şehirli; **Critical Review:** Güzin Özkurt, Nurettin Abacıoğlu, Ahmet Şehirli.

REFERENCES

- Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol.* 2020;92(4):401-2. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475-81. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Nicholas T, Mandaah FV, Esemu SN, Vanessa ABT, Gilchrist KTD, Vanessa LF, et al. COVID-19 knowledge, attitudes and practices in a conflict affected area of the South West Region of Cameroon. *Pan Afr Med J.* 2020;35(Suppl 2):34. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Jahanshahlu L, Rezaei N. Monoclonal antibody as a potential anti-COVID-19. *Biomed Pharmacother.* 2020;129:110337. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Pallotta AM, Kim C, Gordon SM, Kim A. Monoclonal antibodies for treating COVID-19. *Cleve Clin J Med.* 2021 Feb 17. [[Crossref](#)] [[PubMed](#)]
- Parry NMA. COVID-19 and pets: When pandemic meets panic. *Forensic Science International: Reports.* 2020;2100090. [[Crossref](#)] [[PMC](#)]
- Sharun K, Tiwari R, Saied AA, Dhama K. SARS-CoV-2 vaccine for domestic and captive animals: An effort to counter COVID-19 pandemic at the human-animal interface. *Vaccine.* 2021;39(49):7119-22. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Sharun K, Tiwari R, Patel SK, Karthik K, Iqbal Yatoo M, Malik YS, et al. Coronavirus disease 2019 (COVID-19) in domestic animals and wildlife: advances and prospects in the development of animal models for vaccine and therapeutic research. *Hum Vaccin Immunother.* 2020;16(12):3043-54. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. *Front Immunol.* 2020;11:1446. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- LiveScience [Internet]. © Future US, Inc. [Cited: July 1, 2022]. Bryner J. Cat infected with COVID-19 from owner in Belgium. Available from: [[Link](#)]
- Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID-19 induces cytokine storm with high mortality. *Inflamm Regen.* 2020;40:37. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Carlos WG, Gross JE, Cruz CD, Jamil S. Monoclonal antibodies: medical uses for the prevention and treatment of disease. *Am J Respir Crit Care Med.* 2021;203(11):P26-7. [[Crossref](#)] [[PubMed](#)]
- Sharun K, Dhama K. COVID-19 vaccine diplomacy and equitable access to vaccines amid ongoing pandemic. *Arch Med Res.* 2021;52(7):761-3. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Deeks ED. Casirivimab/imdevimab: first approval. *Drugs.* 2021;81(17):2047-55. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses.* 2021;13(4):628. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
- Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ.* 2020;371:m3862. [[Crossref](#)] [[PubMed](#)]

17. Cruz-Teran C, Tiruthani K, McSweeney M, Ma A, Pickles R, Lai SK. Challenges and opportunities for antiviral monoclonal antibodies as COVID-19 therapy. *Adv Drug Deliv Rev.* 2021;169:100-17. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
18. Razonable RR, Pawlowski C, O'Horo JC, Arndt LL, Arndt R, Bierle DM, et al. Casirivimab-Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19. *EClinicalMedicine.* 2021;40:101102. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
19. Bierle DM, Ganesh R, Razonable RR. Breakthrough COVID-19 and casirivimab-imdevimab treatment during a SARS-CoV-2 B.1.617.2 (Delta) surge. *J Clin Virol.* 2021;145:105026. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
20. Nhean S, Varela ME, Nguyen YN, Juarez A, Huynh T, Udeh D, et al. COVID-19: a review of potential treatments (corticosteroids, remdesivir, tocilizumab, bamlanivimab/etesevimab, and casirivimab/imdevimab) and pharmacological considerations. *J Pharm Pract.* 2021;8971900211048139. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
21. Food and Drug Administration. Fact Sheet For Health Care Providers Emergency Use Authorization (Eua) Of REGEN-COV® (Casirivimab and Imdevimab), [Cited: July 10, 2022]. Available from: [[Link](#)]
22. Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol.* 2016;13(1):3-10. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
23. Mizuno T, Kato Y, Kaneko MK, Sakai Y, Shiga T, Kato M, et al. Generation of a canine anti-canine CD20 antibody for canine lymphoma treatment. *Sci Rep.* 2020;10(1):11476. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
24. Van Brussel L, Moyaert H, Escalada M, Mahabir SP, Stegemann MR. A masked, randomised clinical trial evaluating the efficacy and safety of lokivetmab compared to saline control in client-owned dogs with allergic dermatitis. *Vet Dermatol.* 2021;32(5):477-e131. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
25. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. *Science.* 2020;370(6520):1110-5. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
26. World Organisation for Animal Health (WOAH). SARS-CoV-2 in Animals - Situation Report 14. [Cited: June 30, 2022]. Available from: [[Link](#)]