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Use of Anti-Mononuclear Antibodies as Therapy for Covid-19

Jhon Fredy Bello Cordero[1]*, Urbano David Benitez Russo[2], Fernan Andres Torres Hernandez[3], Jesus Miguel Moreno Martinez[4], Mayerly del Carmen Mercado Oliva[5], Daniel Nicolas Pinilla Lopez[6], Miguel Angel Iglesias Herrera[7], Jhoyner Alberto Jimenez Filigrana[8]

1 Medical Specialist Emergency Medicine, Fundacion Universitaria de Ciencias de la Salud Bogota

2 Internist, Universidad Centro Occidental Lisando Alvarado, Venezuela

3 General Physician, Universidad de Cartagena

4 General Physician, Universidad Del Sinu, Montería

5 General Physician, Universidad de Sucre

6 General Physician, Universidad del Rosario, Bogota

7 General Physician, Universidad del Sinu, Cartagena

8 General Physician, Universidad El Bosque, Bogota

***Corresponding author:**
Jhon Fredy Bello Cordero

Jhonbellocordero@hotmail.com

Medical Specialist Emergency Medicine, Fundacion Universitaria de Ciencias de la Salud Bogota

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Abstract

The disease caused by a B-coronavirus, an RNA virus, had its beginnings in 2019 in Wuhan - China where a series of cases of pneumonia caused by this agent were identified, after sequencing the nucleic acid of the epithelial cells of the lower respiratory tract of 4 patients with confirmed pneumonia of unknown cause by real-time reverse transcription PCR at Beijing Hospital, a new beta coronavirus 2019-nCoV, which was later named SARS-CoV-2, was found. Currently there are only maintenance therapies and symptom management, since there are no exact therapies for the management of severe SarsCoV2 infection, antiviral drugs and other drugs used to manage the infection such as acyclovir, panciclovir, chloroquine are used , ganciclovir, remdesivir, nitazoxadine, corticosteroids among other medications currently used for symptom management- The use of neutralizing antibody therapy may alter the course of infection in an infected host, support viral shedding, or protect uninfected hosts exposed to the virus, therefore, this antibody, used alone or in combination, has the potential to prevent and treat COVID-19 and possibly other emerging human diseases caused by the subgenus Sarbecovirus, in addition to being a low-toxic drug and safe. Its use in these patients.

Keywords: Severe Acute Respiratory Syndrome; Viral pneumonia; Coronavirus infections; Antibodies; Cytokines; lymphocytes; Vaccines; COVID-19 Treatment

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Introduction

The disease caused by a B-coronavirus, an RNA virus, had its beginnings in 2019 in Wuhan - China where a series of cases of pneumonia caused by this agent were identified, currently six serotypes that produce diseases in humans are known., four of these are prevalent and cause typical cold symptoms, the remaining two are responsible for the appearance of severe acute respiratory syndrome SarsCoV and Middle East respiratory syndrome MERS-CoV; After nucleic acid sequencing of lower respiratory tract epithelial cells from 4 patients with confirmed pneumonia of unknown cause by real-time reverse transcription PCR at Beijing Hospital, a novel 2019-nCoV beta coronavirus was found, which was then was called SARS-CoV-2, also giving as a result that this new virus has information from the subgenus Sarbecovirus, of the Orthocoronavirinae family, which makes it different from SARS-CoV and MERS-CoV, however according to various reports it was identified that the genome of SARS-Co V-2, is between 75% and 80% identical to SARS-CoV and therefore its name, SARS-CoV-2 belongs to this genus of coronavirus and its genome consists of a single-stranded RNA 29 kb in length. The genome encodes 4 main structural proteins: the so-called spike (S), membrane (M), envelope (E), and nucleocapsid (N).

The last protein is present inside the virion and is associated with the viral RNA, and the other 3 proteins are associated with the external structure of the virus, this disease causing the current pandemic of global importance is characterized by affinity to the respiratory system has characteristics important as the production of increased pro-inflammatory cytokines and a decrease in the response of T cells, which is directly related to inflammation and severe lung damage that occurs in patients infected with SarsCoV2, also highlighting the onset of given symptoms from 5 days, the incubation period of approximately 14 days and the high transmission capacity of the virus given by various mechanisms such as droplet transmission (given when the infected person coughs or sneezes and these droplets released by this mechanism are inhaled by the people nearby), by contact (when an individual has direct contact with contaminated surfaces). inhaled and then passes these through the eyes and mouth) and by aerosols (this occurs when the respiratory droplets of the infected are in contact with the environment in places with little ventilation or closed that when inhaled cause infection), in addition From this, manifestations and alterations have been found in the gastrointestinal area, since enterocytes with high expression of ACE II receptors have been found in this area, which is why fecal transmission is also described in a smaller proportion and less frequently (1). The most affected patients are individuals between 25 and 50 years of age with a mean of 49 years, affecting mostly men and immunosuppressed patients and with the presence of comorbidities such as diabetes mellitus, arterial hypertension, renal dysfunction, liver dysfunction and abnormalities. At the cardiovascular level, there are predominant symptoms of fever, dyspnoea, gastrointestinal manifestations (diarrhoea, decreased appetite, nausea and vomiting), cough, anosmia (loss of smell) secondary to alterations at the level of the olfactory nerve, ageusia (loss of taste) conferred by the high expression of ACE II receptors on the oral mucosa, fatigue, tiredness, urticarial, rashes, acrocyanosis and in more severe cases, septic shock, haemorrhages, coagulopathy and metabolic acidosis may occur [1-3].

Currently there are only maintenance and symptom management therapies, since there are no exact therapies for the management of severe SarsCoV2 infection, antiviral drugs and other drugs used to manage the infection such as acyclovir, panciclovir, chloroquine are used , ganciclovir, remdesivir, nitazoxadine, corticosteroids among other medications currently used for symptom management. In addition to these management alternatives, there is also the use of anti-monoclonal antibodies for the treatment of covid-19, these monoclonal antibodies against SARS-CoV-2 are divided into three groups: 1) antibodies that inhibit the binding and viral entry by targeting virus-specific structures or host receptors, 2) antibodies that interfere with viral replication and/or transcription, and 3) antibodies that block various steps of the immune system response [1, 4]. This therapy is considered one of the innovative findings for the management of this disease, approved by the Food and Drug Administration (FDA), it is about antibodies obtained by means of recombinant DNA technology and hybridoma, which have a capacity to neutralize the receptor binding domain (RBD) [5, 6]. The production of antibodies depends on B cells and once they come into contact with the antigen, these antibodies are identical in specificity, which is why they are called monoclonal antibodies, since they are produced by a single type of B cells from the same cloned or stem cells. Some monoclonal antibodies are currently used to treat COVID-19, standing out in this group itolizumab and tocilizumab, the group's mechanism of action is based on the fact that monoclonal antibodies bind to target molecules, which can be surface membrane receptors, proteins associated with enzymatic systems or circulating proteins, which produces direct or indirect effects on tissue function, where virus neutralization occurs when a sufficient number of epitopes (antigenic determinant is the portion of a macromolecule that is recognized by the immune system, specifically the sequence to which antibodies bind, B cell receptors or T cell receptors.) on the surface of the virus are occupied by antibodies. The occupancy model assumes that obtaining sufficient antibody density in the virus is the most important factor in neutralizing the virus, causing inhibition of binding to cell receptors or interfering with the plasma membrane or endosome fusion process. In addition to this, the antibodies neutralize the infection caused by the virus through their effector function in the Fc region (crystallizable fraction) which is specific for each virus [5, 7]. This alternative represents a great therapeutic option for the management of COVID-19, since it has been shown that it improves the clinical evolution of infected patients, mostly evidenced in adults than, in children, that is, it has use in the population that is affected by most frequently by this agent [6-8]. The use of this neutralizing antibody therapy can alter the course of infection in an infected host, support viral shedding, or protect uninfected hosts exposed to the virus, therefore this antibody, used alone or in combination, has the potential to prevent and treat COVID-19 and possibly other emerging human diseases caused by the Sarbecovirus subgenus, in addition to being a low-toxicity drug and safe to use in these patients [9, 10].

Methodology

To carry out this article, a bibliographic search was carried out in various databases such as Elsevier, Scielo, Medline, PubMed, Science Direct and Ovid, thus selecting original articles, case reports and bibliographic reviews from 2020 to 2022, in Spanish and English. using MeSH terms: Severe Acute Respiratory Syndrome; Viral pneumonia; Coronavirus infections; Antibodies; Cytokines; lymphocytes; Vaccines; COVID-19 treatment and or. Thus including all the documents that will deal with the use of anti-mononuclear antibodies as a therapy for Covid-19, the data found was between 16-28 records, thus using 22 articles for the preparation of this document.

Results

Passive immunotherapy in convalescent plasma or monoclonal antibody preparations has been evaluated for the treatment of COVID-19. The trimetric spike glycoprotein on the viral surface is the main target of the antibody as the spike plays an essential role in allowing the virus to attach to and infect host cells. The SARS-CoV-2 spike glycoprotein is composed of S1 and S2 domains. The S1 domain contains the receptor-binding domain (RBD) that specifically binds to the cellular receptor for human angiotensin-converting enzyme 2 (ACE2), and some RBD-binding antibodies

block the interaction between the RBD and the ACE2 receptor, which leads to neutralization of SARS-CoV-2 infection. Evidence has shown that potent neutralizing monoclonal antibodies that recognize viral RBD are often elicited in SARS-CoV-2 infection. In recent years, highly specific and neutralizing monoclonal antibodies have been successfully isolated against various viruses, serving as an advanced replacement for convalescent plasma in passive immunotherapy. These biologics are now being considered therapies to combat COVID-19 outbreaks. Monoclonal antibodies that target SARS-CoV-2 RBD are being evaluated in outpatients, and trial data suggest that an antibody cocktail of two antibodies, REGN10933 and REGN10987, administered together reduces viral load and related hospital visits. infections in patients with COVID-19 compared to placebo [11,12].

A study from Taiwan, published in 2022 found that representative antibodies targeting non-overlapping epitopes are effective against wild-type virus and recently emerging variants of concern, while encoded by antibody genes with few somatic mutations. Neutralization is associated with inhibition of viral RBD binding to ACE2 and possibly the subsequent fusion process. Structural analysis of representative antibodies, by cryo-electron microscopy and crystallography, reveals that they have some unique aspects that are of potential value while sharing some features in common with previously reported neutralizing monoclonal antibodies. The in vivo efficacy of an antibody cocktail composed of two potent non-competing anti-RBD antibodies was evaluated in a Syrian hamster model. We show that the cocktail prevents weight loss, reduces lung viral load, and attenuates lung inflammation in hamsters in both prophylactic and therapeutic settings. Although the neutralization of one of these antibodies is abrogated by mutations of the B.1.351 variant, it is also possible to produce a bivalent cocktail of antibodies both resistant to variants B.1.1.7, B.1.351 and B.1.617.2 and concluded that neutralizing antibodies target non-overlapping epitopes on the RBD of SARS-CoV-2, which function through mechanisms involving inhibition of receptor attachment and the fusion process. Combination of potent FD-11A and FI-3A exhibits both prophylactic and therapeutic efficacy in a hamster model of SARS-CoV-2 infection and serves as a promising therapeutic cocktail [11] **(Figure 1)**.

Obtained from: Huang KA, Zhou D, Tan TK, et al. Structures and therapeutic potential of anti-RBD human monoclonal antibodies against SARS-CoV-2. Theranostics. 2022; 12(1):1-17. Published 2022 Jan 1. doi:10.7150/thno.65563

Figure 1 the in vivo protection of the FD-11A and FI-3A antibody cocktail against wild-type SARS-CoV-2 in a Syrian hamster model. A, The prophylactic effect of antibody cocktail at 40 mg/kg, 4 mg/kg, and 0.4 mg/kg. A single dose of antibody or control was administered intraperitoneally one day before intranasal virus challenge. b, The therapeutic effect of the antibody cocktail at 40 mg/kg, 4 mg/kg and 0.4 mg/kg. A single dose of antibody or isotopes control was administered intraperitoneally three hours after intranasal virus challenge. Body weight was measured at the indicated time points and the data normalized to the initial weight of each animal. Infectious viral loads in the lungs were measured by the tissue culture median infectious dose (TCID50) assay. Data represent the mean ± standard error of the mean (SEM) (n=4 per group). Anti-influenza The neuraminidase human IgG1 antibody Z2B3 was included as an isotype control.

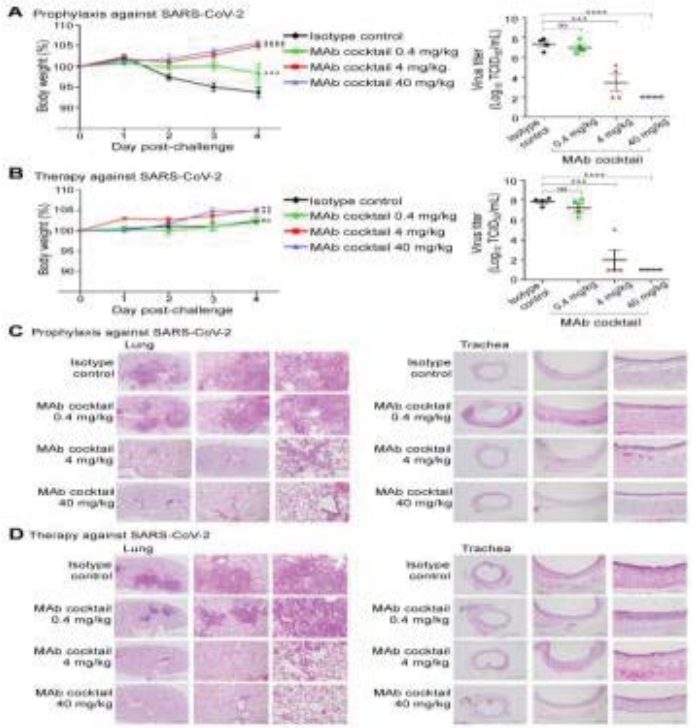

Figure 1 The in vivo protection of the FD-11A and FI-3A antibody cocktail against wild-type SARS-CoV-2 in a Syrian hamster model.

Statistical significance between groups was analyzed using two-way ANOVA and Turkey's post hoc test. The results of the post hoc comparisons between the isotype control and the treatment group were shown in the graph. **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$; ns, not significant. C,D, Histopathological findings of the lungs at (C) prophylactic and (D) therapeutic treatment of the antibody cocktail at 40 mg/kg, 4 mg/kg and 0.4 mg/kg in hamsters four days after infection. By SARS-CoV-2.

In a study conducted in the United States and published in 2022 using a systems analytic approach, they studied peripheral blood samples obtained from patients enrolled in a single institution in the SAC-COVID trial to discern the impact of CD24Fc treatment on the homeostasis. Performing high-dimensional spectral flow cytometry and measuring the levels of a wide range of cytokines and chemokine's to discern the impact of CD24Fc treatment on immune homeostasis in COVID-19 patients; in this it was found that Twenty-two patients were enrolled and the clinical characteristics of the CD24Fc versus placebo groups were matched. Using high-content spectral flow cytometry and network-level analysis, we found that COVID-19 patients had systemic hyper activation. From multiple cellular compartments, including CD8+ T cells, CD4+ T cells, and CD56+ Natural Killer Cells. Treatment with CD24Fc mitigates this systemic inflammation, inducing a return to homeostasis in NK and T cells without compromising the antibody response against Spike protein. Significantly Attenuated CD24Fc Accelerated Systemic Cytokine Response and Decreased Cytokine Co-Expression and Network Connectivity Linked to COVID-19 Severity and Pathogenesis; therefore, they concluded that the data presented here offer immunological insights that underscore the encouraging clinical findings of the SAC-COVID trial. And these results strongly support further investigation of CD24Fc for various infamous conditions, including COVID19. CD24Fc has been tested in Phase II clinical trials to attenuate graft-versus-host diseases and showed promising efficacy, opening up the potential use of this drug in other immune-related diseases [12-14] **(Figure 2)**.

Retrieved from: Song, NJ, Allen, C., Vilgelm, A.E. et al. Treatment with soluble CD24 attenuates COVID-19-associated systemic immunopathology. J Hematol Oncol 15, 5 (2022). https://doi.org/10.1186/s13045-021-01222-y

Figure 2 CD24Fc treatment down regulates systemic cytokine response in COVID-19 patients. Relative differences in plasma concentrations of cytokines/chemokine's between HD (n=25) and patients with COVID-19 (n=22). Values were logarithmically transformed and evaluated using independent sample t-test. Significantly up- and down-regulated markers are shown (A). Heat map analysis (B) visualized the relative levels of cytokines/chemokine's (placebo: D1 n=12, D2 n=12, D4 n=11, D8 n=5; CD24Fc: D1 n=10, D2 n= 10, D4 n=9, D8 n=3). Using log-10 transformation of cytokine concentrations (dots) and GLMM-predicted fixed effect trends (lines), changes in IL-10 (C; p=0.05)

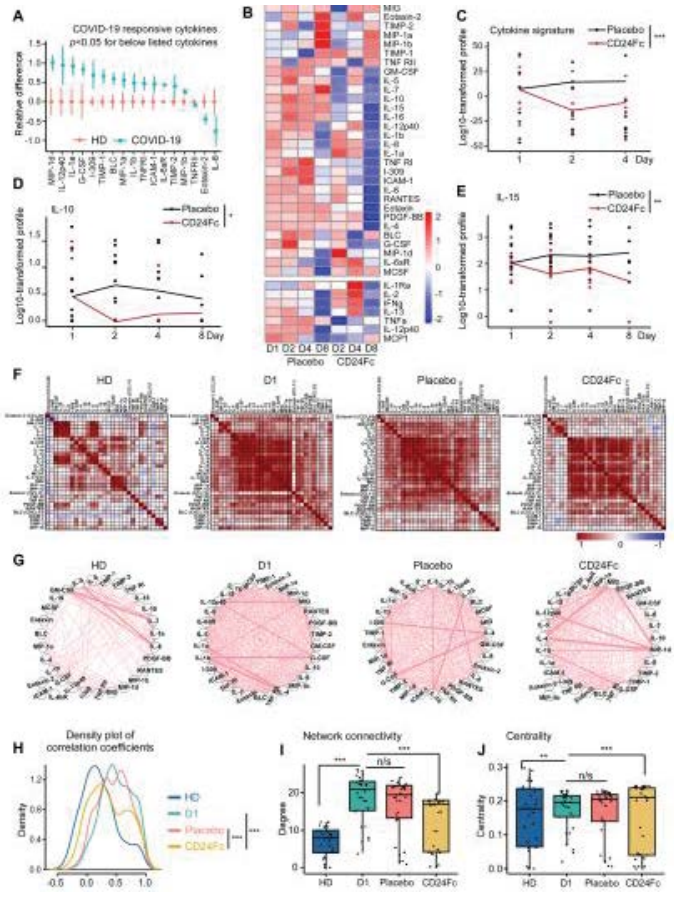

Figure 2 CD24Fc treatment down regulates systemic cytokine response in COVID-19 patients.

and IL-15 (D; p=0.002) in CD24Fc (red) and placebo (black) groups were revealed. Values and trend lines cantered on mean D1. The p value was calculated using the Ken ward-Roger method. Cytokine score was analyzed longitudinally using a weighted sum approach (E; p<0.001). Using Pearson correlation matrices (F) and network maps (G; edge weight represents correlation coefficient), 30 HD plasma markers (n=25), COVID-19 reference (D1, n=22), placebo (pooled D2-D8, n = 28), and CD24Fc-treated groups (pooled D2-D8, n = 24) were visualized. Using these correlation coefficients, a density plot (H; D1 vs. placebo, p=0.07; D1 vs. CD24Fc, p<0.001; placebo vs. CD24Fc, p<0.001). The Kolmogorov-Smirnov test was used to evaluate equality of densities between groups. Connectivity analysis (I) and cytokine network centrality analysis (J) show cytokine expression relationships Network connectivity plots show highly correlated connections for each cytokine (i.e., node degree) and were evaluated using paired t-test. Cytokine network centrality analysis used the eigenvector centrality score that considers global network connectivity and correlation coefficients between cytokines (HD vs. D1, p<0.001; D1 vs placebo, p=0.08; D1 vs CD24Fc, p<0.001). Bartlett's test evaluated the significance of the variance of the centrality scores (HD vs. D1, p = 0.013; D1 vs. placebo, p = 0.17; D1 vs. CD24Fc, p = 0.008). Each point in I and J represents a cytokine. *p<0.05; **p<0.01; ***p<0.001

A study conducted in Iran, which was published in 2022, found that currently in terms of monoclonal antibodies, the main research has focused on exploring mAbs that target the pathogenic protein. The Te S protein is presented on the surface of the coronavirus and plays a vital role in virus entry and induces host immune responses. Previous studies have recognized a variety of mAbs effective in preventing the virus from entering host cells by targeting the SARS-CoV S protein. Depending on the binding site, antibodies that bind to the S protein can inhibit the conformational change of the S protein. protein S and block membrane fusion or block its interaction with ACE2. Therefore, protein S could be considered as a key target to develop effective mAbs against SARS-CoV-2. The critical target of mAbs is RBD (residues n318–510) of protein S [15, 16].

Discussion

Neutralizing monoclonal antibodies are therapeutic tools with great potential for use, since they can be specifically directed to the binding of the receptor (RBD, N318-V510) of protein S or it has also been found that it can bind to the receptor protein ACE2 blocking viral entry in both cases [17], although the immune response is a key factor for the response capacity of patients infected with SARS-CoV-2 and even more so in those who suffer from comorbidities or are in severe stages , as this response is usually diminished, with evidence of lymphopenia and hyper inflammation. It has been shown that age is a risk factor that plays a relevant role related to immunosenescence; and that in young people when there is a reinfection this can aggravate the disease, therefore, the establishment of an adequate treatment in these patients changes the prognosis of life in these age ranges.

The evidence on this type of medication is in continuous development, on the one hand, due to the interesting mechanisms of action and the impact of this pandemic, but without ruling out that the development in many cases of new molecules entails commercial appeal, therefore, it is necessary to keep informed of the new evidence without losing its critical vision and analysis.

In a trial named REMAP-CAP, 56 patients hospitalized for Covid 19 were randomized, of which 28 patients were assigned to the sarilumab cohort and 28 were used as controls (standard care treatment). The results report that by day 28, 61% of patients treated with sarilumab experienced clinical improvement and 7% died. These findings were not significantly different from the comparison group (clinical improvement 64%, mortality 18%) [18].

In a meta-analysis comparing the efficacy of sarilumab versus standard care alone or placebo, there is no evidence of a statistically significant benefit on all-cause mortality at day 28 (RR 0.77, 95% CI 0.43 to 1 .36; 2 RCTs , 880 participants; low certainty), on all-cause mortality at day 60 (RR 1.00, 95% CI 0.50 to 2.0; 1 RCT , 420 participants; low certainty) and serious adverse events (RR 1.17, 95% CI 0.77 to 1.77; 2 RCTs, 880 participants; low certainty [19-22].

Taking this into account, monoclonal antibodies, due to their effectiveness in preventing viral and bacterial infections, or those mediated by toxins, as well as their use in the prevention and post-exposure prophylaxis of pathologies in which the infectious agent has an incubation period and prolonged replication, adding its low rate of adverse effects, and finding ourselves in a growing appearance of germs multi-resistant to antibiotics, it is considered a therapeutic alternative for the treating physician, taking into account that the aforementioned causes us to exhaust the therapeutic alternatives in infectious diseases with high morbidity and mortality, also taking into account that it must be studied in depth to improve its specifications when establishing its treatment.

Conclusion

The SARS-CoV-2 pandemic spread through human-human transmission, and, although the virus identifies ACE2 receptors in epithelial cells of various organs, it is possible that there are increases in antibody-dependent infections (ADEs). Therefore, this aspect should be considered when evaluating vaccines or using monoclonal antibodies, however, the use of these has presented a change in the treatment of Covid.

Antibodies are produced by the body as a defence against disease. However, these can also be made in laboratories from cells taken from people who have recovered from an illness.

Antibodies that are designed to treat or target a specific protein (in this case, a protein from the covid-19 virus) are called "monoclonal", which attach to the covid-19 virus and prevent it from entering and replicate in human cells, which is intended to help fight infection. Monoclonal antibodies have been used successfully to treat other viruses.

An antibody is a protein that is produced naturally by the immune system in response to an infection. A monoclonal antibody is a molecule developed in a laboratory that is designed to mimic or enhance the body's immune system's natural response against

an invader, such as cancer or infection. Monoclonal antibodies have an advantage over other types of infection treatment because they are created to specifically target an essential part of the infectious process. A monoclonal antibody is generated by exposing a white blood cell to a particular viral protein, which is then cloned to mass-produce antibodies that target that virus. Before COVID-19, monoclonal antibodies were developed to treat various viral infections, such as Ebola and rabies.

We found that the use of the antibody can be effective for the elimination of SARS-CoV-2, in patients and even more so in those with a lower initial immune response. The FDA approves the use of these drugs under an emergency authorization in adult patients and in pediatric patients (over 12 years of age) who have moderate disease and who have a high risk of disease progression to severe and that includes hospitalization, for this the FDA highlights the established high risk criteria among which we find: obesity, chronic kidney disease, immunosuppressive treatment, diabetes mellitus, age >65 years, age >55 years with comorbidities and age 12-17 years with comorbidities (obesity, congenital and/or acquired cardiovascular disease, sickle cell anaemia, neurological disorders and asthma, or other respiratory diseases that require daily drug treatment for control).

In the bibliography consulted, it was shown that the toxicity of these drugs is low, and no evidence was found on their toxicity during administration to patients with COVID-19. The evidence on this type of medication is in continuous development, on the one hand, due to the interesting mechanisms of action and the impact of this pandemic, but without ruling out that the development in many cases of new molecules entails commercial appeal, therefore, it is necessary to keep informed of the new evidence without losing its critical vision and analysis.

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