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A review on the updated treatment strategies against SARS-CoV-2

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Abstract: A new beta coronavirus, labelled as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), is the pathogen responsible for this worldwide health concern. There have been 2,616,242 confirmed cases and 449,681 fatalities with SARS-CoV-2. The spread of this epidemic has caused healthcare institutions all around the globe to face various difficulties. The therapeutic methods that deal with COVID-19 infection now rely heavily on supportive measures, such as oxygen supplementation, as well as mechanical ventilation and vaccines, and community-wide infection spread reduction, which are the best weapons we have. The illness is difficult to test and has shown resistance to novel treatment medicines, but drugs that are already known to be safe, effective, and with a defined dose may provide a promising option. While they are neither particular nor exact, they are general. Many of these medicines are undergoing clinical studies, and thus far, their effectiveness and safety have been examined for COVID-19 treatment. While some of these methods need to be validated in rigorous preclinical models and clinical trials, recent research has identified other viable treatment alternatives. The following is a short overview that is meant to highlight the recent developments in combating SARS-CoV-2.

Keywords: SARS-CoV-2, ventilation, drug reposition, clinal trials

INTRODUCTION

SARS-CoV-2 is known for its spherical morphology with surface spikes on the surface. It was shown that SARS-CoV-2 is closely associated with SARS-CoV and bat SL-CoV (SARS-like coronavirus). While SARS-CoV-2 has lesser pathogenicity as compared to SARS-CoV, it also transmits from person to person with greater frequency. The first stage in the cross-species transmission is cell entrance. The SARS-CoV-2 virus is more probable to infect type II alveolar cells in the lungs, might be the reason for the serious alveolar destruction after infection. IFN-α (alpha interferon), chloroquine phosphate, lopinavir/ritonavir, ribavirin, as well as arbidol are advised for antiviral treatment as a new recommendation issued by the NHC (National Health Commission) of the People's Republic of China. Numerous potential strategies have been uncovered as SARS-CoV-2 research progresses, including efforts to inhibit SARS-CoV-2 fusion/entries, block SARS-CoV-2 replication, and suppress extreme inflammation responses, CP treatment (convalescent plasma) and both vaccinations and traditional Chinese treatment combined with Western medicine have been used (as discussed). A series of clinical studies are now underway to evaluate the efficacy as well as safety of potential pharmacological treatments. Here, we examine the present research on the impending therapy of SARS-CoV-2, drawing on the latest findings in the fields of fundamental and clinical research. [1]

POTENTIAL THERAPIES AGAINST SARS-COV-2

The research into novel therapeutic methods which may be used to combat COVID-19 in the future, such as therapeutic agents that are being developed for the treatment of other viral infections, including influenza, MERS-CoV, Ebola, and SARS-CoV virus. Researchers worldwide are doing their best to identify a therapeutic cure for this worldwide epidemic. [2-7]

INHIBITION OF SARS-COV-2 ENTRY/FUSION

Like SARS-CoV, SARS-CoV-2 gains entrance into host cells through the spike (S) protein. Research demonstrated that the S protein of SARS-CoV-2 binds to the host cell's ACE2 (“Angiotensin-Converting Enzyme 2”) receptor, which is an entrance receptor. ACE2 is expected to be more potent in binding SARS-CoV-2 than SARS-CoV. So, attempting to affect the interactions between S protein and ACE2 can be a viable strategy. As a matter of fact, neutralizing antibodies are targeting an RBD (“Receptor Binding Domain”) in the S protein. Due to the similarities between the SARS-CoV-2 S protein and SARS-CoV, the antibody CR3022 which neutralizes SARS-CoV showed strong binding to the SARS-CoV-

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2 RBD. The vast majority of RBD antibody epitopes in SARS-CoV-2, however, had changed significantly when compared to SARS-CoV, according to Song and Zheng, necessitating the development of a new batch of monoclonal antibodies for SARS-CoV-2. Furthermore, the decision to target the ACE2 receptor as a particular molecule has been thoroughly discussed in other studies. There is a current clinical study underway, randomized, open-label, controlled, and pilot study, which is further exploring the effects of rhACE2 (recombinant human ACE2; GSK2586881) in serious cases of COVID-19 (Clinical Trials Reg No. NCT04287686). Researchers claimed that S protein entrance into cells depends on ACE2 as well as the host cell's serine protease TMPRSS2. Camostat mesylate, which has shown efficacy in blocking TMPRSS2 and therefore limiting SARS-CoV-2 lung cell infection, may serve as a potential COVID-19 therapy. Further, the cell membrane and SARS-CoV-2 viral fusion involves HR1 (Heptad Repeat 1) as well as HR2 (Heptad Repeat 2). Xia et al. revealed that two fusion inhibitors developed from HR2-derived peptides (HR2P) as well as EK1 (updated OC43-HR2P peptide) showed excellent fusion inhibitory action against SARS-CoV-2 and work as entry/fusion inhibitors to fight against SARS-CoV-2 viral. More research is needed to confirm these theories. [8-12]

In addition, the claim was made that coronavirus entrance was also reliant on pH and receptor-specific endocytosis. An alternative option to combat SARS-CoV-2 is targeting endocytosis. Clathrin-mediated endocytosis is controlled by the host enzyme AAK1, which is related to the AP-2 protein kinase family. The artificial intelligence (AI) technique was used to seek a set of authorized medicines that target AAK1. Although the kinase inhibitor baricitinib, which blocks AAK1, was anticipated to be a potential COVID-19 therapy, its normal dosage was adequate to fully impede AAK1. [7, 9-12]

According to the list of NHC guidelines, the treatment of COVID-19 now has two more potential therapeutic alternatives: Arbidol and chloroquine phosphate. Arbidol was proven to block the entrance and fusion of the viral membranes with the cell membranes by preventing numerous viruses from getting into the cells. Traditional antimalarial medication chloroquine exhibited its *in vitro* efficacy against the SARS-CoV-2 virus. Chloroquine phosphate is being tested in many clinical studies to determine its effectiveness and safety against COVID-19. Chloroquine phosphate was more successful in preventing the progression of pneumonia than control therapy, as reports from more than 100 cases had demonstrated. However, we still do not know the molecular mechanism behind the chloroquine phosphate for COVID-19 treatment. It has been said that chloroquine may hinder late-stage viral replication or endosome-mediated viral entrance. A more intense effort must be applied to uncover the precise process. [7-8]

SARS-COV-2 REPLICATION DISRUPTION

Several antiviral drugs were produced to combat polymerases, proteases, entry proteins, as well as MTases. A variety of antiviral medicines are being tested in clinical studies, including favipiravir (Chinese Clinical Trial Reg No. ChiCTR2000029544 & ChiCTR2000029600), arbidol (ChiCTR2000029621), Remdesivir (Clinical Trials Reg No. NCT04257656 & NCT04252664), lopinavir/ritonavir (ChiCTR2000029387, ChiCTR2000029468, & ChiCTR2000029539), and ASC09 (ChiCTR2000029603). Remdesivir, which Martinez said was the most effective antiviral to combat SARS-CoV-2, was discovered. Remdesivir is an adenosine analog monophosphorami [1] date prodrug. The RdRps (RNA-dependent RNA polymerases) activity incorporates its active form into nascent viral RNA, which subsequently causes RNA synthesis to cease. Wang et al. have shown that remdesivir suppressed SARS-CoV-2 efficiently *in vitro*. The patient's clinical status improved after receiving intravenous remdesivir in the first COVID-19 case discovered in the USA. Ribavirin as well as favipiravir are monophosphoramidate prodrugs of guanine analogs and were authorized for various viral illnesses treatment. In the case of COVID-19, however, its antiviral effects will require more evidence to back them up. The protease inhibitors ritonavir as well as lopinavir target the coronavirus primary proteinase (3CLpro; 3C-like protease). The polypeptide translation result is processed by 3CLpro from the genomic RNA into protein components. The primary viral protease was also targeted in the clinical drug libraries with the use of high-throughput screening. Tegobuvir, nelfinavir, bictegravir, and prulifloxacin are four molecules that demonstrated acceptable binding conformations with the infection primary protease. [13-19]

Another strategy for combating SARS-CoV-2 is targeting the RNA genome. Nguyen et al. demonstrated the utility of a new CRISPR/Cas13 RNA knockdown method by using it to cleave the SARS-CoV-2 RNA genome. Such CRISPR/Cas13d method has been comprised of the protein Cas13d as well as a guide that is precisely complementary to the viral RNA genome with RNA spacer sequences. Cas13d was proposed to be administered to the lungs infected with SARS-CoV-2 through an AAV ("Adeno-Associated Virus"). [15, 17-21]

THE SUPPRESSED EXCESSIVE INFLAMMATORY RESPONSE

To respond effectively to infection, the host immune system requires a coordinated cytokine response. However, a dysfunctional response in certain SARS-CoV-2 infected individuals may lead to a hyperinflammatory state. ICU patients with COVID-19 reported having greater cytokines levels in their plasma than non-ICU individuals, signifying that the cytokine storm is linked with the severity of the illness. In addition, higher levels of GM-CSF^{+} (granulocyte-macrophage

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colony-stimulating factor-positive) and IL-6^{+} (interleukin-6-positive) CD4^{+} T was seen in SARS-CoV-2 infected ICU individuals compared to those non-ICU individuals. Considering this, a way to deal with COVID-19 may be to block excessive inflammatory responses. Despite this, there is debate over the use of corticosteroids, which shows good pharmacological benefits to suppress an exuberant and dysfunctional inflammatory system. According to the current NHC recommendation, systemic corticosteroids should not be used unless a justification for their prescription is provided. According to current evidence, it seems that corticosteroid therapy offers little benefit to SARS-CoV or MERS-CoV patients. This may be due to the immune system's suppression of its ability to fight off infection. It was also shown that in a group of severely sick patients with SARS-CoV-2, therapy with corticosteroids at a modest dosage may help the overall situation. More research is required to determine the appropriate use of corticosteroids. [22-35]

siRNA

siRNA ("small interfering RNA") is a kind of double-stranded RNA molecule that is found in a range of 20 to 25 base pairs in length. siRNAs can manage the expression of specific genes through RNA interference (RNAi). Therapeutic methods for antiviral, anticancer, and genetic disorders have been developed and used, all of which are based on siRNA-based techniques. Research in the past has shown that siRNA-based medicines against MERS-CoV as well as SARS-CoV were successful because of the use of siRNAs targeting viral RNA-dependent RNA polymerase, the nucleoprotein, protease, as well as N helicase. Therefore, this technique must be considered for use in treating COVID-19 to improve therapy results and decrease the risk of viral pandemics. [22-35]

SPHINGOSINE MIMICS

S1P ("Sphingosine 1-phosphate") lipid mediator has several cellular functions. A set of immunosuppressants known as sphingosine mimics may be utilized in some infectious illnesses. They may mimic sphingosine receptor agonists, which lead to lymphopenia by inducing the lymphocytes to be sequestered in the lymph nodes, resulting in immunosuppression. Research has revealed that mice infected with influenza exhibit a therapeutic response to S1P. They observed that the administration of the S1P agonist directly into the trachea resulted in reduced lung damage and the generation of pro-inflammatory cytokine. This kind of treatment, therefore, may be used in the reduction of COVID-19-related CRS. Even yet, when it comes to therapy, targeting pro-inflammatory immune cells may not be effective since it reduces the host's ability to remove the viral infection. Using S1P analogs in conjunction with antiviral medication should be done with care since it ensures that the virus is completely eradicated. [22-36]

NUCLEAR FACTOR-KAPPA B INHIBITORS

SARS-Cov-2 tends to activate NF-kB (nuclear factor-kappa B), which is one of the reasons why it is more severe. COVID-19 patients have an increased susceptibility to CRS, and NF-kB encourages the development of cytokine-encoding genes, which increases CRS risk. Additionally, NF-kB may activate the platelet activator receptor, which greatly increases the chance of forming deep vein thrombosis in the peripheral capillaries. As well, the NF-kB signaling pathway has been shown to lead to the synthesis of GTPase (specialized for transporting RNA polymerase II into the nucleus), which is a crucial factor in the mRNA transcription for SARS-CoV-2. As a result, we need to limit the activity of NF-Kb by utilizing a drug like Amlexanox™, which is a well-known NF-Kb inhibitor. [37]

CYTOKINE RECEPTORS FC-FUSION PROTEINS

As an antibody-like decoy, cytokine receptors Fc-fusion proteins are also a possible therapeutic option for COVID-19-infected individuals, according to recent studies from Cambridge University. To design specific cytokine receptors, such as some interleukin and interferon receptors, the scientists used a novel protein modification tool named QTY code, which enables them to swap hydrophobic amino acids with hydrophilic ones. The QTY variant cytokine receptors have many comparable physiological characteristics to those of the original receptors, however, they do not have the hydrophobic parts. To create an antibody-like structure, the receptors have been fused to the Fc region of IgG protein. COVID-19-infected individuals with severe CRS have a much more elevated inflammatory response that can be treated with a short-acting, Fc-fusion decoy treatment approach based on QTY code design functional, water-soluble Fc-fusion structures. [22-35]

REGULATORS OF THE INTESTINAL MICROECOLOGY

In addition to respiratory symptoms such as fever, dyspnea, and cough, the primary symptoms of individuals with COVID-19 include headaches and less frequent symptoms such as gastrointestinal problems including diarrhea, nausea,

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and vomiting. It's interesting to note that many individuals began their illness with symptoms in the gastrointestinal tract. Previous statements have made it clear that SARS-CoV-2 interacts with ACE2 receptors, which are found in healthy people's lungs and intestines, as well as in the epithelia of both organs. The researchers found that exposure of the small intestine's epithelial cells to foreign pathogens elevated the ACE2 expression. Changes in the intestinal microecology may be due to mutations in the ACE2 receptor, resulting in lower production of antibacterial peptides in intestinal cells. Researchers thus assumed that the ACE2 receptor might have an impact on the intestinal flora of COVID-19. A recent study suggests that usage of microecological regulators (regulates intestinal flora) may decrease the chance of enteritis and respiratory-related lung infection; it may therefore be employed to treat serious cases to preserve the microbial balance in the intestines and to prevent subsequent bacterial viruses. While no clinical evidence exists to date suggesting the use of microecological regulators in the intestinal tract may has crucial involvement for COVID-19 treatment, the therapeutic option is still a possible choice or could be utilized as an adjuvant. [38-40]

DRUGS TARGETING THE HOST INTERACTOME OF SARS-COV-2

The COVID-19 virus has a host interactome, a therapeutic model that is increasingly used to target genes that the virus needs to grow and replicate. This strategy depends on the assumption that treating a serious viral infection with a short-term treatment period of inhibiting these host functions will not cause serious harm. This model aims to identify the molecular features of pathogenic phenotype in SARS-CoV-2 viral by using a network-based approach. The novel design will allow the structure-guided study to help discover new host targets, perhaps paving the way for improved pharmaceutical as well as diagnostic studies. In addition, it was discovered that utilization of drug-gene interactions in molecular docking to identify antiviral medicines is a significant aid in the search for novel therapeutic methods, including single and combination drug treatments, in the fight against the COVID-19 pandemic illness. [25, 27, 39-41]

CONCLUSION

Many studies on coronaviruses have been done throughout the years, yielding a variety of treatment options. In the future, such findings are likely to be applied to SARS-CoV-2 or any other emerging coronavirus. We believe that, like SARS and MERS, this pandemic epidemic will diminish in a few months as a result of ongoing worldwide efforts to prevent SARS-CoV-2 spread. Nonetheless, this epidemic emphasises the critical need to develop and produce novel coronavirus treatment methods. Currently, our primary focus must be on implementing infection control measures to prevent COVID-19 from spreading further throughout the world, while also increasing vaccination.

REFERENCES

[1] Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA (2020) Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Path 9:186

[2] Pal M, Berhanu G, Desalegn C, Kandi V (2020) Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 12:e7423

[3] Pachetti M, Marini B, Benedetti F, Giudici F, Mauro E, Storici P et al (2020) Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependentRNA polymerase variant. J Transl Med 18:179

[4] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ et al (2020) Research development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci 6:315–331

[5] Guo G, Ye L, Pan K, Chen Y, Xing D, Yan K et al (2020) New insights of emerging SARS-CoV-2: epidemiology, etiology, clinical features, clinical treatment, and prevention. Front Cell Develop Biol 8:410–425

[6] Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P (2020) Enhancing immunity in viral infections, with special emphasis on COVID-19: a review. Diabetol Metab Syndr 14:367–382

[7] Lima WG, Brito JM, Overhage J, Nizer W (2020) The potential of drug repositioning as a short-term strategy for the control and treatment of COVID-19 (SARS-CoV-2): a systematic review. Arch Virol 2:1

[8] Chen Y, Wang A, Yi B, Ding K, Wang H, Wang J et al (2020) The epidemiological characteristics of infection in close contacts of COVID-19 in Ningbo city. Chin J Epidemiol 41:20–29

[9] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G et al (2020) A trial of lopinavirritonavir in adults hospitalized with severe Covid-19. N Engl J Med 7:1787– 1799

[10] Khalili JS, Zhu H, Mak N, Yan Y, Zhu Y (2020) Novel coronavirus treatment with ribavirin: groundwork for an evaluation concerning COVID-19. J Med Virol 92:740–746

[11] Tong S, Su Y, Yu Y, Wu C, Chen J, Wang S et al (2020) Ribavirin therapy for severe COVID-19: a retrospective cohort study. Int J Antimicrob Agents 56: 106–114

[12] Lou Y, Liu L, Qiu Y (2020) Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled. Trial Med Rxiv 1:4

[13] Lou Y, Liu L, Yao H, Hu X, Su J, Xu K et al (2021) Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. Eur J Pharm Sci 157: 105631

[14] Wu R, Wang L, Kuo HD, Shannar A, Peter R, Chou PJ et al (2020) An update on current therapeutic drugs treating COVID-19. Curr Pharm Rep 1:15

[15] Dabbous HM, Abd-Elsalam S, El-Sayed MH, Sherief AF, Ebeid FF, Abd El Ghafar MS et al (2021) Efficacy of favipiravir in COVID-19 treatment: a multicenter randomized study. Arch Virol 166:949–954

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[16] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H et al (2020) First case of 2019 novel coronavirus in the United States. N Engl J Med 382: 929–936
[17] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A et al (2020) Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 11:2327–2336
[18] Nojomi M, Yassin Z, Keyvani H, Makiani J, Roham M, Laali A et al (2020) Effect of Arbidol (Umifenovir) on COVID-19: a randomized controlled trial. BMC Infect Dis 20:954
[19] Schrezenmeier E, Dörner T (2020) Mechanisms of action ofhydroxychloroquine and chloroquine: for rheumatology. Nat Rev Rheumatol 16:155–166
[20] Joh RG, Peter AN, Paul AF, Michael JA (2020) Urgent guidance for navigating and circumventing the QTC-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID19). JMCP Mayo Clin Proc 3:24–36
[21] Sultana J, Cutroneo PM, Crisafulli S, Puglisi G, Caramori G, Trifirò G (2020) Azithromycin in COVID-19 patients: pharmacological mechanism, clinical evidence and prescribing guidelines. Drug Saf 43:691–698
[22] Pania A, Lauriola M, Romandinia A, Scaglione F (2020) Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. Int J Antimicrob Agents 10:6053
[23] Russo V, Puzio G, Siniscalchi N (2006) Azithromycin-induced QT prolongation in elderly patient. Acta Biomed 77:30–32
[24] Kezerashvili A, Khattak H, Barsky A, Nazari R, Fisher JD (2007) Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. J Interv Card Electrophysiol 18:243–246
[25] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM (2012) Azithromycin and the risk of cardiovascular death. N Engl J Med 366:1881–1890
[26] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J et al (2020) Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis 34:101663
[27] Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M (2016) Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 42:829–840
[28] Li Q, Li W, Jin Y, Xu W, Huang C, Li L et al (2020) Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. Infect Dis Ther 9:823–836
[29] Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA et al (2020) Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 8:267–276
[30] Wang D, Hu B, Hu C, Zhu F, Peng Z (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel corona virus–infected pneumonia in Wuhan, China. J Am Med Assoc 323:1061–1069
[31] Ling Y, Xu S, Lin Y, Zhu Z (2020) Persistence and clearance of viral RNA in 2019 novel corona virus disease rehabilitation patients Chinese. Med J 133:9
[32] Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P et al (2020) Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med 7:170–186
[33] Fang L, Karakiulakis G, Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 32:171–189
[34] Gurwitz D (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 1:4–19
[35] Nejat R, Sadr S (2021) Are losartan and imatinib effective against SARS-CoV2 pathogenesis? A pathophysiologic-based in silico study. In Silico Pharmacol 9:1
[36] Bengtson CD, Montgomery RN, Nazir U, Satterwhite L, Kim MD, Bahr NC et al (2021) An open label trial to assess safety of losartan for treating worsening respiratory illness in COVID-19. Front Med 8:630209
[37] Izurieta HS, Chillarige Y, Kelman JA, Forshee R, Qiang Y, Wernecke M et al (2018) Statin use and risks of influenza-related outcomes among older adults receiving standard-dose or high-dose influenza vaccines through medicare during 2010-2015. Clin Infect Dis 67:378–387
[38] Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, Rayego-Mateos S, Santos Sanchez L, Marchant V et al (2020) Statins: could an old friend help in the fight against COVID-19? Br J Pharmacol 177(21):4873–4886
[39] Lin S, Chen Y, Lin Y, Hsieh Y, Wang S, Lin Y et al (2007) Pravastatin induces thrombomodulin expression in TNFα-treated human aortic endothelial cells by inhibiting Rac1 and Cdc42 translocation and activity. J Cell Biochem 101:642–653
[40] Dong L, Hu S, Gao J (2020) Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 14:58–60
[41] Fu B, Xu X, Wei H (2020) Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med 18:164–178