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Full Length Article

Treatment of COVID-19 by monoclonal antibodies and the traditional Chinese medicine



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ABSTRACT

The mortality rate of the recent global pandemic corona virus disease 2019 (COVID-19) is currently as high as 7%. The SARS-CoV-2 virus is the culprit behind COVID-19. SARS-CoV-2 is an enveloped single-stranded RNA virus, the genome encodes four types of the structural proteins: S protein, E protein (envelope protein), M protein (matrix protein) and N protein (nucleocapsid protein). In COVID-19, monoclonal antibodies have played a significant role in diagnosis and treatment. This article briefly introduced the development of monoclonal antibodies targeting on S protein and N protein, which represents the main direction of monoclonal antibody drugs used in the diagnosis and treatment of COVID-19. Meanwhile, the traditional Chinese medicine also plays important role in the fight against COVID-19 by regulating human immunity. The article introduced the use of traditional Chinese medicine in fighting against COVID-19.

1. Introduction

The mortality rate of the recent global pandemic COVID-19 is currently as high as 7%. The SARS-CoV-2 virus is the culprit behind COVID-19 [1]. Patients infected with SARS-CoV-2 always have severe acute respiratory syndrome and Middle East respiratory syndrome similar to MERS-CoV [2]. More seriously, COVID-19 infection is accompanied by a severe inflammatory response caused by the release of excessive cytokines such as TNF- α , interleukins IL-6 and IL-1, resulting in a so-called cytokine storm (CS). Thus, a vigorous host immune response that recruits macrophages, lymphocytes, neutrophils, and T cells against virus-infected cells leads to this hyper-inflammatory state. Worse, multiple organ failure and lung damage will happen after that [3]. Therapeutic strategies for managing COVID-19 CS are expected to reduce virus-related mortality and morbidity [4].

Monoclonal antibody (mAbs) is produced by artificially prepared hybridoma cells. The production process can be summarized as injecting the antigen into the immunized animal to produce antibodies and then combining the antibody with myeloma cells to produce hybridoma cells, the resulting hybridoma cells are screened, and the antibody-producing hybridoma cells are cloned and amplified, and finally purified to obtain monoclonal antibodies. Therefore, mAbs are also defined as laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on

target cells by binding to antigens found on the surface of cells [5].

Currently, 217 therapeutic antibody programs targeting COVID-19 have entered the development stage. 133 programs target S protein which contains 3 groups of antibody therapies that have been approved by Emergency Use Authorization (EUA) for the treatment of COVID-19 patients. 79 programs are in clinical trials (Phase I/II/III) of which 25 target the S protein. 66 programs are in early stage, including 60 in preclinical stages. In conclude, at least 29 countries and 291 companies/institutions are developing antibody therapies against the COVID-19 [6].

2. Monoclonal antibodies used on COVID-19

2.1. The structure of the novel coronavirus

SARS-CoV-2 is an enveloped single-stranded RNA virus characterized by a spike protein, the S protein, with a club-like protrusion on the surface of the virus. The SARS-CoV-2 genome encodes four types of the structural proteins: S protein, E protein (envelope protein), M protein (matrix protein) and N protein (nucleocapsid protein) [7]. The S protein on the surface of SARS-CoV-2 mediates the binding and fusion of the virus with the host cell membrane receptor (Fig. 1). And the N protein is an RNA-binding protein with a high degree of basicity and various activities in SARS-CoV-2. As the most abundant protein helping the virus to infect cells, the N protein plays an indispensable role in the infection and

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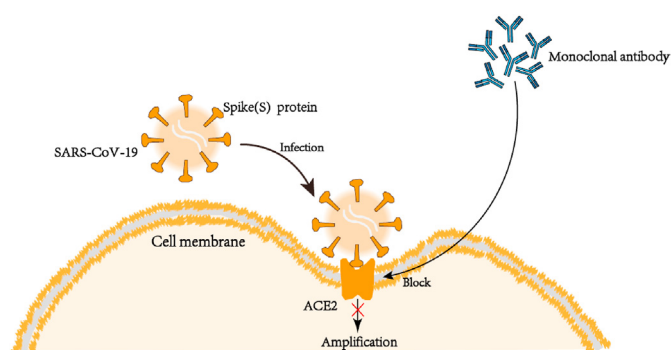


Fig. 1. Mechanism of COVID-19 infection blocked by monoclonal antibodies.

replication of SARS-CoV-2 regarded as a structural protein that assembles viral genomic RNA into nucleocapsids and virions, and as a regulatory protein that promotes viral transcription and replication and suppresses host innate immune responses [8].

The monoclonal antibody drugs currently being put into clinical phase II/III trials are mainly the S protein-based monoclonal antibody drugs, and the N protein-based types are still in the research stage.

2.2. S protein-based monoclonal antibody drugs

The spike-like S protein of SARS-CoV-2 is the most important surface protein of the virus, determining the host range and specificity of SARS-CoV-2. The S protein is also a key target for neutralizing antibodies (NAbs) and vaccine design [9]. The first step of SARS-CoV-2's invading cells is the interaction of the S protein on the virus surface with the receptor on the surface of the host cell [10]. The S protein mainly completes the invasion process through the interaction of the RBD receptor with ACE2. If the process of the S protein's binding to the ACE2 receptor could be effectively blocked, the invasion of SARS-CoV-2 can be effectively prevented. So most neutralizing antibodies target the receptor-binding epitope of RBD [10] and produce a competitive inhibitory effect with the RBD receptor, thus exerting a neutralizing effect (Fig. 1).

So far, many types of drugs have entered Phase II/III clinical trials, it is hopeful that monoclonal antibody drugs will be put into the treatment of COVID-19 in the near future (Table 1) [10]. In 2020, the US FDA issued Emergency Use Authorization (EUA) for two monoclonal antibodies (Casilizumab and Imdevimab) against the SARS-CoV-2 spike protein which can block viral binding and reduce the occurrence of escaping mutants [11]. Nonetheless, the FDA reported that Casilimab and Imdevimab were not permitted for patients hospitalized or requiring oxygen therapy for COVID-19 [12,13]. In 2021, the U.S. FDA issued EUAs

for Bamlanivimab and Etesevimab for adults and children with mild or moderate symptoms but high risks of severe infection [14]. In addition, the FDA granted single-agent emergency use authorization of Sotrovimab for nonhospitalized patients (age >12 years, weight >40 kg) with mild or moderate symptoms but high risks of disease progression. Eteletzvirumab is the second anti-COVID-19 neutralizing antibody drug in the world entering the clinical trial research stage. The combination therapy of Banivirumab and Eteletzvirumab can more effectively reduce the viral load. In terms of safety, the combination therapy was well tolerated with no drug-related serious adverse events (SAEs) and low rates of treatment emergent adverse events (TEAEs) when compared with placebo [10]. Due to its excellent therapeutic effect, monoclonal antibody drugs targeting the S protein were put into clinical phase II/III trials in various countries and even put into emergency use in the United States. Despite the fact that monoclonal antibody drugs' side effects exist and their prices are high due to their high development cost, the drugs which target the S protein can cope with advanced symptoms and will become members of the first-choice drugs for the treatment of COVID-19 in the future.

2.3. N protein-based monoclonal antibody drugs

The N protein, also known as nucleocapsid protein, has a high degree of sequence conservation and RNA chaperone activity, which makes it an antagonist of interferon and an inhibitor of virally-encoded RNA interference [21]. The N protein is the main structure of the virus, which is a basic protein composed of 419 amino acids and has a short lysine-rich protein. The N protein is highly immunogenic and has fewer mutations over time than the spike and envelope proteins, which makes it a good target for detection [22–24]. After the virus infects human cells, the N protein will be expressed in large quantities which induces humoral and cellular immune responses [25,26]. In addition, N proteins are involved in the transcription and replication of viral mRNAs, tissue cytoskeleton and immune regulation and regulation of cellular metabolism and cell cycle [27,28]. Therefore, the N protein can be used in vaccine development, serological detection and as a marker protein for virus detection [29]. The process of monoclonal antibodies' production is as follows. Firstly, synthesize the gene encoding the N protein according to the published whole genome sequence of the nucleic acid of the new coronavirus Secondly, realize the recombinant expression of the N protein in the *Escherichia coli* system by constructing a vector. And then inject the recombinant N protein into the body of the immunized animal. Next, extract the spleen cells of the immunized mice and obtain the hybridoma monoclonal cell lines which can secrete the antibody that specifically binds to the N protein through hybridoma cell fusion technology and subcloning screening method. Finally, the monoclonal antibodies can be put into large-scale production [22]. In the future, the N protein monoclonal antibody can be fully applied to immunological immunization platforms such as immunochromatographic test strips and biosensors,

Table 1
Summary of major neutralizing antibodies in clinical trials against SARS-CoV-2.

Company	Product	Antibody type	Clinical trial stage	Test number
REGN/NIAID	REGN-COV2 [15]	Human IgG1 monoclonal antibody targeting the S protein	Clinical Phase II/III	NCT04452318 NCT04426695 NCT04425629
LILLY/AbCellera/NIH	Banivirumab [16]	Human IgG1 targeting the S protein Monoclonal antibodies	Clinical Phase II/III	NCT04497987 NCT04634409 NCT04518410
LILLY/Institute of Microbiology Chinese Academy of Sciences/Shanghai Junshi Biological	Eteletzvirumab/Banivirumab [17,18]	Human IgG1 targeting the S protein Monoclonal antibodies	Clinical Phase II/III	NCT04427501
Vir Biotechnology/GSK	VIR-7831/GSK4182136 [19]	Human IgG1 targeting the S protein Monoclonal antibodies	Clinical Phase III	NCT04545060
AstraZeneca/Vanderbilt	AZD8895/AZD1061 [20]	Human IgG1 targeting the S protein Monoclonal antibodies	Clinical Phase III	NCT04507256
Institute of Microbiology Chinese Academy of Sciences/Shanghai Junshi Biological	Atelimumab (JS016) [10]	Human monoclonal antibodies targeting epitopes of the S protein	Clinical Phase II	NCT04441918

which has positive implications for achieving a fast, highly sensitive diagnosis of COVID-19.

2.4. Monoclonal antibody drugs currently used in the treatment of COVID-19 and their efficacy evaluation

Ambavirumab injection (BRII-196) and Romisevirumab injection (BRII-198) with longer half-lives were isolated from hundreds of strains of human monoclonal antibodies against novel coronavirus (SARS-CoV-2). Then they were screened and regarded as neutralizing antibodies for the treatment of COVID-19 in early 2020 [30]. Ambavirumab injection (BRII-196) and Romisevirumab injection (BRII-198) can clinically reduce the risk of hospitalization and death by 80% [30]. Nearly 900 patients also showed neutralizing activities against the mutant strains that appeared. A total of 847 patients were recruited worldwide in this clinical trial of combination therapy with all the subjects being randomized 1:1, and finally 837 patients entered the antibody treatment group ($n = 418$) or the placebo group ($n = 419$). Interim results showed that the combination of Ambavirumab/Romisevirumab reduced the composite endpoint of hospitalization and death in COVID-19 outpatients at high risk of clinical progression by 78% compared to placebo [30]. The final analysis data of the phase III clinical trial study showed that the risk of hospitalization and death of patients treated with Ambavirumab injection (BRII-196) and Romisevirumab injection (BRII-198) was reduced by 80%. There were no deaths in the treatment group during the 28-day treatment period, while there were 9 deaths in the placebo group [31].

In conclusion, the approval of the combination therapy of Ambavirumab injection (BRII-196) and Romisevirumab injection (BRII-198) largely meets the clinical needs of patients infected with COVID-19 in our country. The combination therapy of Ambavirumab injection (BRII-196) and Romisevirumab injection (BRII-198) is likely to make my country deal with the complex and changeable COVID-19 epidemic more calmly.

3. Traditional Chinese medicine in the treatment of COVID-19

Chinese medicine has been shown to be effective in the treatment of COVID-19, and also plays an important role in relieving patients' early discomfort and reducing the rate of referral for serious illness. In China, patients with COVID-19 have had good results at different stages of treatment with Chinese herbal compounds, either alone or in combination with western drugs.

According to the Pneumonia Treatment Protocol for Novel Coronavirus Infection, COVID-19 is a plague in TCM, with the disease located in the lung, and the pathogenesis can be summarized as "dampness, heat, toxicity and blood stasis" [32]. The clinical treatment in TCM can be divided into five stages: the mild stage (cold-damp constraint in the lung pattern, damp-heat accumulation in the lung pattern); the moderate stage (damp-toxin constraint in the lung pattern, cold-damp obstructing the lung pattern); the severe stage (epidemic toxin blocking the lung pattern, blazing of both qi and yin pattern); the critical stage (internal blockage and external desertion pattern) and the recovery stage (lung-spleen qi deficiency pattern, deficiency of both qi and yin pattern) [32].

Currently, the traditional Chinese medicine Lianhua Qingwen is the mainstream treatment for COVID-19. According to the clinical research results, the treatment effect of Lianhua Qingwen on COVID-19 was significantly higher than that of the control group [OR = 3.34, 95% CI (2.06, 5.44), $P < 0.001$]; The disappearance rate of other clinical secondary symptoms is significantly higher than the control group [OR = 6.54, 95% CI (3.59, 11.90), $P < 0.001$]. The duration of fever was significantly lower than that of the control group [OR = -1.04, 95% CI (-1.60, -0.49), $P < 0.001$] [33]. It can be seen that Lianhua Qingwen has played a good role in the treatment of both mild and severe cases, and also has certain advantages in relieving cough and fever.

It can be speculated that in the future the combined treatment of traditional Chinese medicine and western medicine is an important

direction for the treatment of COVID-19. That is, the use of targeted drugs such as monoclonal antibodies to directly kill the virus or block the virus invasion and the use of traditional Chinese medicine to regulate human body and treat the patient's symptoms can achieve comprehensive treatment, and also alleviate the adverse reactions caused by western medicine to the patient.

4. Conclusion

In the fight against the new coronavirus pneumonia—COVID-19 pandemic, the effect of monoclonal antibody drugs is undoubtedly remarkable, and the development prospect is undoubtedly optimistic. However, its variability is worthy of attention at present for SARS-CoV-2 is an RNA virus. It will not be enough if the monoclonal antibody drug only targets two structural proteins. In addition, there are also a large number of reports of serious side effects or severe immune reactions after monoclonal antibody therapy. Therefore, monoclonal antibodies' risk assessment must be put on the agenda. Furthermore, whether monoclonal antibodies can have more accurate targeting and whether traditional Chinese medicine can be used in combination with monoclonal antibody drugs to reduce the side effects are still needed to be explored.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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