Original Article

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Clinical and Immunological Considerations of Monoclonal Antibody Therapy in COVID-19: A Review

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Abstract

Currently, effective methods for the prevention and treatment of coronavirus infections have not been developed. This could be attributed to the unique pathogenesis of the coronavirus infection and the rapid global spread of the pandemic, which have posed challenges to ongoing research efforts. Similar to other viral infections, coronavirus infection leads to the development and dissemination of the inflammatory process, resulting in viremia or the systemic spread of the infection. This uncontrolled inflammatory response is characterized by elevated levels of cytokines such as IFNy, IL-1, IL-6, and IL-12 in the bloodstream, transitioning the initial inflammatory reaction into a phase known as the cytokine storm. The cytokine storm is marked by severe clinical and laboratory manifestations. Consequently, it is crucial to implement appropriate therapies that target the uncontrolled inflammation induced by the virus rather than viremia itself. Hence, the aim of our study was to investigate the impact of monoclonal antibodies, specifically the medication "Kazirivimab + Imdevimab," which is a combination of recombinant monoclonal antibodies targeting the S-protein, on the clinical progression and laboratory parameters in patients with COVID-19.

Keywords: monoclonal antibodies, interleukin-6, Covid-19.

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Introduction

Despite nearly two decades of studying pathogenic coronaviruses (CoV), effective methods for preventing and treating diseases caused by them have not yet been developed. This situation may be attributed to the unique characteristics of CoV pathogenesis and the rapid progression of the pandemic, which have posed challenges to the effectiveness of ongoing research. The emergence of the coronavirus infection, known as COVID-19 (short for COronaVIrus Disease), in late 2019 and early 2020 led to its widespread outbreak, affecting numerous countries worldwide. Consequently, the World Health Organization (WHO) declared the outbreak as a global CoV pandemic.[1,2,3] COVID-19 is characterized by high contagiousness with a relatively low risk of infection. the mortality rate is in the range of 1-6%.[4,5,6,7,8,9] As is known, the primary gateway of infection is the single-layer epithelium of the pulmonary alveoli, where the virus can enter in five different ways.[10,11,12,13,14] The most typical way is through binding of the CoV spike protein (SP) to the angiotensin-converting enzyme (ACE) receptor.[2,8] In addition to ACE, CD147, also known as BASIGIN, plays a certain role in the process of SARS-CoV invasion.[11,15,16,17] The outer membrane of the virus that has entered the endosome merges with the endosomal membrane and releases viral RNA into the cytoplasm, where virus replication, virion assembly, and a whole cascade of events occur, accompanied by the formation of an inflammatory response.[1,13,14] Order II alveolocytes are rapidly responding cells that express and secrete proinflammatory cytokines. Along with the secretion of IL-6, TNFα, IL-1β, IL-8, part of the alveolar epithelium undergoes pyroptotic death, the products of which are absorbed by granulocytes, monocytes/macrophages. Migrated poly - and mononuclears, in turn, are activated for further secretion of pro-inflammatory cytokines and chemokines; simultaneously with the activation of inflammatory cells, an increase in the permeability of interstitial capillaries is observed, which leads to plasma leakage from them and the formation of local edema.[16,18,19] As the inflammatory process develops and spreads, the virus infects dendritic cells and various subpopulations of mononuclear phagocytes. This creates conditions for the development of viremia, that is, generalization of infection, cytokine secretion becomes uncontrolled, and the concentration of IFNγ, IL-1, IL-6, IL-12 in the blood serum significantly increases, in other words, the primary inflammatory reaction passes into a new phase — the cytokine storm phase.[6,7,18] Clinically, this is manifested by hyperthermia, dry cough, an increase in respiratory failure that turns into acute respiratory distress syndrome (ARDS), signs of nephropathy develop, and increasing hemodynamic disorders and coagulopathy phenomena are accompanied by the formation of disseminated intravascular coagulation (DIC).[9,10,12,15]

In connection with the above, adequate therapy aimed at stopping the uncontrolled process induced not so much by viremia as by the associated immune inflammation is of crucial importance.

This implies a well-defined hypothesis, in our opinion, that anti-inflammatory treatment, including those aimed at suppressing the cytokine storm, may be a higher priority for patients with COVID-19 from the point of view of survival than direct therapy aimed at eliminating the virus. One of the solutions to this problem may be the use of immunomodulatory therapy that can inhibit excessive inflammatory responses, thus restoring homeostatic regulation of impaired regulatory functions.[20]

In this regard, the aim of our study was to study the effect of monoclonal antibodies, in particular the drug "Kasirivimab + Imdevimab"— a combination of recombinant monoclonal antibodies directed against S-protein on the clinical course and laboratory data in patients with a new coronavirus infection –Covid-19.

Subjects and Methods

We conducted a study involving 38 patients, aged 31 to 57 years (mean age 44.2±5.3 years), who had a mild to moderate course of novel coronavirus infection. The duration of their illness was no more than 3 days. Random sampling was used to divide the patients into two groups. The main group (n=19) received a combination of therapies, including antiplatelet (75 mg/day of acetylsalicylic acid), anti-inflammatory (1000 mg/day of paracetamol), antioxidant (5% ascorbic acid, 10.0 ml/day), and a combination of monoclonal antibodies, specifically the drug "Kazirivimab 1200 mg/ml + Imdevimab 1200 mg/ml," administered intravenously via drip, as a one-time treatment. The comparison group (n=19) also received antiplatelet, anti-inflammatory, antioxidant, and antiviral (Remdesivir 100 mg according to the recommended regimen) therapy in accordance with the temporary treatment guidelines for COVID-19. A control group consisting of 10 healthy individuals was also included. The immune system status was assessed before treatment and on the fifth day of treatment by measuring interleukin-6, procalcitonin, ferritin, D-dimer, and C-reactive protein levels in the blood serum. Interleukins, procalcitonin, and D-dimer were measured using enzyme-linked immunosorbent assay kits manufactured by Vector-Best (Novosibirsk). Ferritin levels were determined by Immunoturbidimetry, and CRP levels were measured using standard clinical methods. The data obtained was processed using Microsoft Excel software and the built-in "Analysis Package" designed for statistical analysis.

Results & Discussion

The initial data of patients in both groups were comparable ($p>0.05$) and demonstrated a significant increase in IL-6, ferritin, CRP, and D-dimer levels in the blood serum. Among these indicators, IL-6 exhibited the most prominent increase. IL-6 is known for its pro-inflammatory properties and its ability to activate and attract white blood cells in response to infection. Previous studies have associated elevated IL-6 levels with a new coronavirus infection, suggesting the presence of persistent viral infection in these patients. Our findings align with these studies and indicate that, in the early stages of the disease, an elevated IL-6 level serves as an early indicator of the onset of inflammation, even in the absence of clinical symptoms.

The inclusion of a combination of recombinant monoclonal antibodies, specifically the drug "Kazirivimab + Imdevimab," in the treatment regimen demonstrated clinical efficacy by preventing the onset of clinical symptoms. In patients presenting with symptoms of upper respiratory tract inflammation (such as runny nose, throat irritation, and sore throat), these symptoms disappeared within 2-3 days of treatment without the need for antiviral or antibacterial drugs. In the main group, IL-6 levels significantly decreased ($p<0.05$) by the control period (5 days after starting therapy) with the drug "Kazirivimab + Imdevimab." Conversely, changes in these indicators in the control group were less pronounced and statistically insignificant [Table 1].

While the ferritin content tended to decrease, the levels of CRP and D-dimer initially showed an increasing trend in the early stages of the disease but returned to normal range by the control period. In the comparison group, these indicators showed less significant changes and were statistically unreliable. Additionally, the comparison group exhibited a slight increase in CRP and ferritin levels, along with an increase in clinical signs of upper respiratory tract inflammation. Therefore, in the comparison group, the inclusion of antibacterial and glucocorticosteroid therapy became necessary based on individual indications.

The incorporation of the drug "Kazirivimab + Imdevimab" as part of the comprehensive therapy led to an earlier and significant decrease in IL-6 levels [Table 1].

Table 1: Dynamics of immunological and clinical parameters in the blood during treatment.

#	Indicators	Main group (n= 19)		Comparison group (n=19)		Control group (n=10)
		Before	After	Before	After	
1	IL-6 (pg / ml)	14,16+2,7	9,07 +0,8*	14,9+1,5	19,18+2,3*,**	5,3 + 0,2
2	Ferritin (pg / ml)	592,3+8,6	435,2+9,8*	578,5+8,4	575,2+9,1*,**	154,6 + 5,1
3	D-dimer (pg / ml)	1,15+0,02,02	0,27+0,01*	1,1+0,02	1,01+0,01*,**	0,31 + 0,03
4	CRP	5,8+1,7	3,1+1,5*	5,9+1,7	8,3+1,2*,**	2,75+0,3

Note:

*-the level of confidence of the initial data $p< 0.05$,

* * - data confidence level between groups $p< 0.05$.

When evaluating clinical data such as hyperthermia, aches, headaches, and sore throat, the main group showed normalization of the temperature response as early as on the 2nd day of monoclonal antibody administration, sore throat

persisted for 3-4 days, and aches and headaches stopped as early as on the 2nd and 3rd days. In the comparison group, hyperthermia was observed up to 4-5 days, sore throat persisted up to 5 days, headache and aches periodically manifested on the 4th and 5th days.

Conclusion

The study provided evidence of the beneficial effects of monoclonal antibodies when administered during the early stages of the disease. This was reflected in the absence or disappearance of clinical symptoms, a significant reduction in interleukin-6 levels, and a tendency towards decreased ferritin, D-dimer, and CRP in the blood. The findings suggest that monoclonal antibodies act rapidly and specifically to disrupt the inflammatory cascade, thereby eliminating the need for antiviral and antibacterial drugs. In contrast, the comparison group showed a tendency towards increasing laboratory markers and the persistence of some symptoms of illness, further underscoring the effectiveness of monoclonal antibodies. These initial positive results emphasize the importance of further exploring the mechanisms of action of monoclonal antibodies in the comprehensive treatment of COVID-19 and their potential for preventive use.

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