Original Article

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Clinical and Immunological Aspects of the Use of Monoclonal Antibodies in the New Coronavirus Infection Covid-19

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Abstract

To date, methods of prevention and treatment of coronavirus infections have not been developed in essence. One of the reasons for this situation may be the peculiarities of the pathogenesis of coronavirus infection and the rapid development of the pandemic, which could hinder the effectiveness of ongoing research. As with any viral infection, with the development and spread of the inflammatory process, viremia develops, that is, the generalization of infection, cytokine secretion becomes uncontrolled, and the concentration of IFNy, IL-1, IL-6, IL-12 in the blood serum significantly increases, in other words, the primary inflammatory reaction enters a new phase — the cytokine storm phase, which manifests itself violently even according to clinical and laboratory parameters. In this regard, adequate therapy aimed at stopping the uncontrolled process induced not so much by viremia as by the associated inflammation is crucial. In this regard, the aim of our study was to study the effect of monoclonal antibodies, in particular the drug "Kazirivimab + 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.

Keywords: Monoclonal Antibodies, Interleukin-6, Covid-19.

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Introduction

Despite the almost twenty-year history of pathogenic CoV, methods for their prevention and treatment of diseases caused by them have not been developed to date. One of the reasons for this situation may be the peculiarities of the pathogenesis of CoV infection and the rapid development of the pandemic, which could hinder the effectiveness of ongoing research. The outbreak of coronavirus infection (CoV), called COVID-19 (an abbreviation for the words COronaVIrus Disease) in late 2019 and early 2020, became widespread and affected most countries of the world, which served as the basis for the World Health Organization (WHO) to declare a 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] 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.[6,7] The most typical way is through binding of the CoV spike protein (SP) to the angiotensin-converting enzyme (ACE) receptor.[2,8,9,10] In addition to ACE, CD147, also known as BASIGIN, plays a certain role in the process of SARS-CoV invasion.[11] 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.[1,12,13,14] 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.[15,16,17,18,19] 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.

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.[19]

Subjects and Methods

We examined 38 patients with mild and moderate course of novel coronavirus infection aged from 31 to 57 years (44.2±5.3 years), with a disease duration of no more than 3 days. 2 groups were formed by random sampling. Patients of the main group (n=19) received antiplatelet (acetylsalicylic acid 75 mg/day), anti-inflammatory (paracetamol 1000 mg/day), antioxidant (ascorbic acid 5% -10.0 ml/day) therapy, as well as a combination of monoclonal antibodies, the drug "Kazirivimab 1200 mg/ml + Imdevimab 1200 mg / ml " intravenously, drip, once. The comparison group (n=19) also received antiplatelet, anti-inflammatory, antioxidant, antiviral (Remdesivir 100 mg according to the scheme) therapy in accordance with the temporary standards for the treatment of the new coronavirus infection Covid-19. As a control, 10 practically healthy individuals were examined. The state of the immune system was assessed before treatment and on the fifth day of treatment by the following indicators: changes in the content of interleukin-6, procalcitonin, ferritin, D-dimer, C-reactive protein in blood serum. The content of interleukins, procalcitonin, and D-dimer was determined by enzyme-linked immunosorbent assay. Reagent kits for the enzyme - linked immunosorbent assay of human cytokines manufactured by Vector-Best (Novosibirsk) were used. The study of ferritin in the blood was carried out by Immunoturbidimetry. The content of CRP was studied by general clinical methods. The obtained data is processed on a personal computer, in the Microsoft Excel software environment using the built-in "Analysis Package", specially designed for solving statistical problems.

Results & Discussion

The initial data in patients of both groups were comparable ($p>0.05$) and were characterized by a significant increase in the content of IL-6, ferritin, CRP, and D-dimer in the blood serum of patients. At the same time, the increase in IL-6 was more pronounced compared to other compared indicators. It is known that IL-6 belongs to the group of pro-inflammatory interleukins by its properties, and is able to cause activation and chemotaxis of white blood cells in response to infection. A number of researchers describe the association of elevated serum IL-6 levels in patients with a new coronavirus infection, explaining this by the presence of persistent viral infection in this category of patients. The data obtained by us correlate with the results of these studies and allow us to conclude that in the early stages of the disease with a new coronavirus infection, outside of clinical manifestations, an increase in the content of IL-6 is an early indicator of the onset of the inflammatory process. The effectiveness of treatment with the inclusion of a combination of recombinant monoclonal antibodies-the drug "Kazirivimab + Imdevimab" was clinically manifested by the absence of the onset of clinical symptoms. As well as in patients with signs of catarrhal inflammation of the upper respiratory tract (rhinorrhea, tickling and sore throat), the symptoms disappeared on 2-3 days of treatment, without the use of antiviral and antibacterial drugs. The content of IL-6, against the background of the drug "Kazirivimab + Imdevimab" by the control period (5 days after the start of therapy) in the main group significantly decreased ($p<0.05$). Changes in these indicators in the control group were not so pronounced and were unreliable [Table 1].

The ferritin content tended to decrease. The content of CRP and D-dimer initially tended to increase in the early stages of the disease, but by the control period, the content of these indicators was within the normal range. Changes in the same indicators in the comparison group were not so pronounced and were unreliable. In addition, in the comparison group, there was a slight increase in CRP and Ferritin levels, and the clinical signs of catarrhal inflammation of the upper respiratory tract increased. In this regard, in addition to treatment after the 5th day, it was necessary to include antibacterial, as well as glucocorticosteroid therapy for individual indications.

The inclusion of the drug "Kazirivimab + Imdevimab" in the complex therapycontributed to an earlier and significant decrease in the content of interleukin-6 [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

Thus, the study demonstrated a positive effect of using monoclonal antibodies in the early stages of the disease, which was manifested by the absence or disappearance of clinical signs of the disease, a significant decrease in interleukin-6, as well as a tendency to reduce ferritin, D-dimer, and CRP in the blood. The data described above show that monoclonal antibodies react instantly, purposefully disrupting the further cascade of inflammatory reactions, and also makes it possible to dispense with the use of antiviral and antibacterial drugs. The indicators of the comparison group, which by the control period showed a tendency to increase laboratory data and preserve some symptoms of intoxication, once again confirmed the effectiveness of the use of monoclonal antibodies. The obtained preliminary positive results dictate the need for further study of the mechanisms of influence of monoclonal antibodies in the complex therapy of the new coronavirus infection Covid-19 and the possibility of their preventive use.

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