Original Article

ISSN (0): 2635-0815; ISSN (P): 2635-0823

Efficiency of Monoclonal Antibodies Application against Covid-19

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Abstract

Despite the 20 years history of pathogenic coronavirus infection, methods of prevention and treatment of diseases caused by this infection were not developed yet. One of the reasons could be the features of pathogenesis and a quick spread of the pandemic which may have made researches more complicated. As an inflammatory process develops, a generalization of infection also develops. A cytokine secretion becomes rockets up, Interferon-γ (IFN-y), interleukin-1(IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), concentration increases. To put it in other words, the primary inflammatory reaction enters a new phase — the cytokine storm phase. In this regard, adequate therapy aimed at stopping the uncontrolled process induced not so much by viremia as by the inflammation associated with it becomes crucial. Therefore, the aim of our research was to study the impact of monoclonal antibodies, in particular the drug "Kazirivimab + Imdevimab" — a combination of recombinant monoclonal antibodies aimed against S-protein on the clinical course and laboratory data in patients with a new coronavirus infection – Covid-19.

Keywords: New Coronavirus Infection, COVID-19, monoclonal antibodies, interleukin-6.

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Received: 15 February 2022 **Revised: 07 March 2022** **Accepted: 16 March 2022** **Published: 13 April 2022**

Introduction

Coronavirus infection (CoV), which is named COVID-19 (COrona VIrus Disease), spread out all over the world in the end of 2019 and beginning of 2020 year and this made World health organization (WHO) declare a CoV pandemic.[1,2] COVID-19 is highly contagious and has low mortality level of 1-6%.[3,4] Despite the 20 years history of pathogenic coronavirus infection, methods of prevention and treatment of diseases caused by this infection were not developed yet. One of the reasons could be the features of pathogenesis and a quick spread of the pandemic which may have made researches more complicated. As it is known, the primary gateway of infection is the single-layer epithelium of the pulmonary alveoli, where the virus can be introduced in five different ways.[5,6,7] The binding of spike protein (SP) CoV to the angiotensin converting enzyme (ACE) receptor is considered to be the most typical.[8,9] In addition to ACE, CD147, also known as BASIGIN, plays a certain role in the process of SARS-CoV invasion.[10] The outer membrane of the virus that has penetrated the endosome merges with the endosomal membrane and releases the virus RNA into the cytoplasm, where virus replication, virion assembly and a cascade of events occur, accompanied by the formation of an inflammatory response.[11,12,13] The primary responding cells, where expression and subsequent secretion of proinflammatory cytokines occur, are second-order alveolocytes. Along with the secretion of interleukin-6, interleukin-1β, interleukin-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 proinflammatory 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.[14,15] As the inflammatory process develops and spreads, the virus infects dendritic cells and various subpopulations of mononuclear phagocytes. At the same time, conditions are created for the development of viremia, that is, the generalization of infection, cytokine secretion becomes uncontrolled, and the concentration of IFNγ, IL-1, IL-6, IL-12 increases significantly in the blood serum, in other words, the primary inflammatory reaction enters a new phase — the cytokine storm phase.[16,17,18] Clinically, this is manifested by hyperthermia, dry cough, an increase in respiratory failure, turning into acute respiratory distress syndrome (ARDS), signs of nephropathy develop, and increasing hemodynamic disorders and coagulopathy are accompanied by the formation of disseminated intravascular coagulation (DIC).[19]

Therefore, adequate therapy aimed at stopping the uncontrolled process induced not so much by viremia as by the inflammation associated with it becomes crucial.

Hence, in our opinion, a well-defined hypothesis that anti-inflammatory treatment, including those aimed at suppressing the cytokine storm, for patients with COVID - 19 may be a higher priority 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 reactions, thus restoring homeostatic

regulation of impaired regulatory functions.

Consequently, a purpose of our research was examination of influence of monoclonal antibodies, particularly of drugs "Kasirivimab + Imdevimab" – a combination of recombinant monoclonal antibodies, aimed against S-protein on the clinical course and laboratory data in patients with a new coronavirus infection – Covid-19.

Subjects and Methods

32 patients with mild and moderate course of new coronavirus infection aged from 32 to 57 years (44.5 ± 5.2 years), with a disease duration of no more than 3 days, were examined. Two groups were formed by random sampling. Patients of the main group (n=15) 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" in/in, drip, once. The comparison group (n=17) 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 a new coronavirus infection Covid-19. For comparasion, 10 practically healthy individuals were examined. The state of the immune system was assessed before treatment and on the fifth day of treatment according to 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 solid-phase enzyme immunoassay. Sets of reagents for enzyme immunoassay of human cytokines of the company "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 data obtained was processed on a personal computer, in the Microsoft Excel software environment using a built-in "Analysis Package" specially designed for solving statistical problems.

Results

Initial data of patients from both groups were comparable (p>0,05) and characterized by significant rise in content of IL-6, ferritin, SRP, D-dimer in patients' blood serum. Additionally, rise in IL-6 was more expressed to compare with other comparing indicators. It's known that, IL-6 with its properties relates to the group of proinflammatory interleukins, and is able to trigger activation and chemotaxis of leukocytes in response to infection. Connection of high level IL-6 in blood serum of patients with new coronavirus infection described by a number of researchers, explaining it with presence of persistent virus infection in this category of patients. Received data correlate with this study's results and allow us to conclude, that in early stages of new coronavirus infection disease, not in clinical manifestation, rise of IL-6 content appears to be early indicator of initial inflammatory process. Effectiveness of treatment, including combinations of recombinant monoclonal antibodies, that is a drug "Kaziriimab + Imdeimab", clinically manifested with absence of manifestation beginning of clinical symptoms. Furthermore, for patients with catarrh of the upper respiratory tract signs (rhinorrhea, sore throat), the symptoms disappeared for 2-3days of treatment, without application of antiviral and antibacterial drugs. IL-6 content significantly decreased (p<0,05), on the background of the "Kaziriimab + Imdeimab" drug in general group. Changes in this indicators were inaccurate and not too expressed in control group (Table 1).

Content of ferritin had downward trend. Content of S-reacting protein (SRP) and D-dimer initially at the early stage of disease had upward trend, but the content of these indicators were within normal limits by control date. Changes of these indicators in comparison group were inaccurate and not too expressed. In addition, there was some increase in indicators of SRP, ferritin, clinical sign of catarrh of the upper respiratory tract increased in comparison group. Because of that, in addition to treatment after 5th day, the antiviral, antibacterial and also glucocorticosteroid therapy were included by individual readings.

Inclusion of complex therapy with "Kaziriimab + Imdeimab" drug helped to reduce content of interleukin-6 earlier [Table 1].

Table 1: Dynamics of immune and clinical indicators in blood on the background of treatment

No	Indicators	Main group (n= 15)		Comparison group (n=17)		Control group (n=10)
		Before	After	Before	After	
1	IL-6 (pg/ml)	13,16+2,7	9,77 +0,8*	14,7+1,5	19,8+2,3*,**	5,3 + 0,2
2	Ferritin (pg/ml)	587,3+8,6	450,2+9,8*	568,5+8,4	565,2+9,1*,**	154,6 + 5,1
3	D-dimer (pg/ml)	1,1+0,02	0,29+0,01*	1,2+0,02	1,5+0,01*,**	0,31 + 0,03
4	SRP (g/l)	5,3+2,7	3,2+1,5*	5,8+1,7	8,2+1,2*,**	2,75+0,3

Note:

*- the level of reliability of the source data p< 0,05,

**- the level of reliability of the data between groups p< 0,05.

Conclusion

Accordingly, research has showed positive effect of using

monoclonal antibodies at early stages of disease, which manifested by absence or disappearance of clinical signs of disease, significant decrease of interleukin-6, and also with downward trend of ferritin, D-dimer, SRP in blood.

Data described above shows, that monoclonal antibodies react instantly, purposefully disrupting the cascade of inflammatory reactions, also give opportunity to recover without application of antiviral and antibacterial drugs. Indicator of comparison group, that had upward trend by the control period again validated effectiveness of using monoclonal antibodies. Received in advance positive results tell about necessity of further study on influencing mechanisms of monoclonal antibodies in complex therapy of new coronavirus infection Covid-19 and opportunities of preventive application.

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How to cite this article: Erkin A, Sayyora B, Ziyovuddin S. Efficiency of Monoclonal Antibodies Application Against Covid-19. Adv Clin Med Res. 2022;3(2): 10-12.

Source of Support: Nil, **Conflict of Interest:** None declared.