West Kazakhstan Medical Journal
Volume 66, Issue 4, DOI 10.18502/wkmj.v66i4.17780
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Research Article

Interleukin-6 Inhibitor Olokizumab in Hospitalized Adults with Moderate COVID-19: Results of a Single Center Observational Study

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Abstract

A single-center observational study was performed to evaluate the effectiveness and safety of the interleukin-6 inhibitor olokizumab in hospitalized adults with moderate COVID-19. This study enrolled 337 patients aged from 22 to 96 years old. After the administration of olokizumab, there was a significant reduction in body temperature, decrease in CRP, and an increase in the levels of blood cells. Revealed clinical improvement was seen in 69.7% of cases, 8.5% of patients showed deterioration in their condition and were transferred to the ICU, 13.6% died. Olokizumab was well tolerated except for slight elevation in live enzymes, such as aspartate transaminase and alanine transaminase.

Keywords: COVID-19, C-reactive protein, interleukin-6, olokizumab

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Received: 19 February 2024
Accepted: 21 May 2024
Published: 20 December 2024

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1. Introduction

The outbreak of novel coronavirus disease 2019 (COVID-19) has swept almost every country and become a global public health threat. For more than 4 years, the whole world has been fighting with COVID-19. According to current WHO data, 70,26,465 deaths from COVID-19 and 77,44,69,939 cases of COVID-19 have been registered [1, 2]. In the autumn of 2023, a surge in coronavirus infection was again detected. Despite the milder course of COVID-19 now, people continue to die from it. So, 10,068 deaths from COVID-19 were reported in the last month [1].

At this time, after the end of the pandemic, several questions were still unanswered, and one of the most important was the choice of effective and safe treatment for patients with severe COVID-19. Severe forms of SARS-CoV-2 infection are characterized by excessive production of pro-inflammatory cytokines, which leads to a phenomenon known as a “cytokine storm”. There is a significant increase in the level of cytokines such as interleukin-6 (IL-6) and other proinflammatory mediators [3]. Elevated serum cytokines, IL-6 in particular, are associated with enhanced mortality in hospitalized COVID-19 patients as the hyperergic immune response can result in progressive lung damage and coagulopathy [3–5]. A number of clinical trials with IL-6 inhibitors, such as tocilizumab, proved the efficacy of IL-6 pathway blockade for the clinical course of the disease [6–7]. However, other studies of tocilizumab have not shown improvements in COVID-19 outcomes with this drug [3–4].

Olokizumab, a humanized monoclonal antibody belonging to the IgG4κ isotype, selectively binds to human IL-6 and effectively neutralizes the effect of this proinflammatory cytokine [8]. The drug has a unique action mechanism since it directly binds IL-6 and thus blocks the pathological cascade of inflammatory reactions. In this, it differs from tocilizumab, sarilumab, and levilimab, which are antagonists of the IL-6 receptor [8]. Due to the high affinity for IL-6 and the mode of action (inhibition of the interaction between IL-6 and the glycoprotein gp130), the pharmacodynamic effects of olokizumab are realized at lower doses [8]. Results of a number of small noncomparative clinical trials have demonstrated a positive effect of olokizumab in patients with moderate COVID-19, primarily with body temperature and a decrease in laboratory parameters of inflammatory activity [8–12].

However, despite the positive aspects of the olokizumab use, a number of authors consider routine therapy with IL-6 inhibitors in COVID-19 to be inappropriate [13]. A significant disadvantage of this therapy is the risk of developing infectious diseases. It is also important that there is still not enough convincing data on the clinical effectiveness of olokizumab in patients with COVID-19 [13]. Given the above, we performed our study to evaluate the effectiveness of olokizumab in hospitalized patients with moderate COVID-19 and pneumonia in real-world clinical practice.

2. Methods

This prospective noncomparative observational study was conducted in the multidisciplinary hospital, in Moscow, Russia, from June 21 to July 20, 2021. Adults aged 18 and older who were polymerase chain reaction (PCR)-positive for SARS-CoV-2 and had pneumonia confirmed by a chest CT scan, who have signed an informed consent form, were recruited within 24 hours of admission. Patients with severe/critical COVID-19 who were hospitalized directly to the ICU were not eligible for the study. Exclusion criteria were also known as hypersensitivity to olokizumab, active bacterial infectious diseases (including tuberculosis), pregnancy, and breastfeeding.

Olokizumab was given to patients in accordance with the current national clinical guidelines, especially if there was lung parenchyma involvement and at least two additional factors revealed: fever for at least 3 days, elevated serum C-reactive protein (CRP) by at least 6 times UNL, decreased SpO_2(<97%) with dyspnea, blood lymphocytes ≤1.5 x 10^9/L, or leukocytes ≤3.5 x 10^9/L.[6] Olokizumab was administered intravenously in a dose ranging from 64 to 128 mg; an additional dose was allowed when insufficient effect was seen within 24 hours (the maximum dose was 256 mg).

Along with olokizumab, all the patients received standard therapy, including dexamethasone, antivirals, anticoagulants, and respiratory support. In addition to routine PRC tests, AmpliTest SARS-CoV-2 VOC v.2" (series CVGL4) was applied in a subset of patients for detecting RNA coronavirus and SARS-CoV-2 genetic lines Alpha, Beta/Gamma and Delta based on the determination of their characteristic mutations in S gene by PCR (Registration certificate # P3H 2021/14907, issued by Roszdravnadzor, Russia).

For each patient demographic data, concomitant diseases, vital signs, chest CT scan findings, and lab tests were recorded at baseline; body temperature and selected laboratory markers–blood leukocytes, lymphocytes, thrombocytes count, serum CRP, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate transaminase, and alanine transaminase were reevaluated in 24–48 hours after the drug exposure. Outcomes such as clinical improvement during the hospital stay, transfer to ICU due to COVID-19 progression, and in-hospital mortality were recorded.

The data were analyzed using R v.3.3.2 free software environment for statistical computing and graphics (The R Foundation for Statistical Computing, Vienna, Austria) and presented for numerical variables as mean, standard deviation (SD), minimum and maximum values (normal distribution) or median and interquartile range (25^{th}–75^{th} percentile) in case of abnormal distribution, qualitative variables— as absolute and relative rates. Samples belonging to the normal distribution were checked by applying the Kolmogorov–Smirnov criteria. When comparing groups, nonparametric methods were used (Wilcoxon-test, chi-square test, or Fisher exact test). All differences were considered to be statistically significant when the p-value was less than 0.05 in two-tailed tests.

3. Results

In total, 337 patients, mean age 62.6+14.5 years old, 60.5% females, were enrolled. Baseline characteristics of the patients are presented in Table **1**. The mean duration of COVID-19 symptoms was 8.1+2.4 (1.0-15.0) days. Altogether 191 (56.0%) patients received 64 mg of olokizumab,121–128 mg (35.5%), 14–192 mg (4.1%), and 16– 256 mg (4.7%).

Table 1: Baseline characteristics and outcomes in hospitalized adults with COVID-19.

Parameter	Value
Number of patients	337
Age, years	62.5 ±14.5 (22.0; 96.0)
Female, n/%	204/60.5
Main comorbidities	
Arterial hypertension, n/%	193/57.4
Obesity, n/%	150/44.7
Diabetes mellitus, n/%	59/17.4
Coronary artery disease, n/%	58/17.1
Malignancy, n/%	22/6.5
Atrial fibrillation, n/%	20/5.9
Chronic heart failure, n/%	19/5.6
Lungs involvement	
1 stage (<25% of the lung), n/%	99/31.0
2 stage (25-50% of the lung)	160/50.2
3 stage (>50% and ≤75% of the lung)	54/16.9
4 stage (>75% of the lung)	6/1.9
Respiratory support, n/%	337/100
Low flow oxygenation, n/%	261/77.4
High flow oxygenation, n/%	21/6.2
Noninvasive ventilation, n/%	13/3.8
Invasive mechanical ventilation, n/%	42/12.5
Outcomes	
Clinical improvement, n/%	262/77.7
Transfer to ICU, n/%	29/8.6
In-hospital mortality, n/%	46/13.6

After the administration of olokizumab, there was a significant reduction of body temperature revealed as well as a rapid and highly significant decrease in CRP (Table **2**). On the contrary, LDG value increased from 621 IU/L to 662 IU/L. An increase in the level of blood cells was observed and the proportion of patients with leukopenia, lymphocytopenia, and thrombocytopenia decreased.

The mean duration of hospital stay was 7.7+4.0 days varying from 3 to 26 days. Clinical improvement was seen in 238 (69.7%) cases, 29 (8.5%) patients showed deterioration in their condition, and, therefore, were transferred to the ICU, and 46 (13.6%) died. After olokizumab administration, a slight elevation of

Table 2: The effect of olokizumab on body temperature and laboratory tests in hospitalized patients with COVID-19 (n=337).

Parameter	Baseline [Me (Q25; Q75)]	24-48 hours After Drug Expose [Me (Q25; Q75)]	P value
Body temperature, ^{0}C	37.9 (37.2; 38.5)	36.5 (36.3; 36.7)	<0.0001
C-reactive protein, mg/l	71.0 (42.5; 114.5)	12.0 (5.0; 25.0)	<0.000001
Total leukocytes, x10^9/L	5.1 (3.8; 6.7)	6.8 (5.1; 8.8)	<0.000001
Leukopenia*, n/%	96/28.5	36/11.1	<0.00001
Total lymphocytes, x10^9/L	0.8 (0.6; 1.1)	1.0 (0.7; 1.5)	<0.000001
Lymphopenia**, n/%	220/66.1	152/49.2	<0.00001
Total thrombocytes, x10^9/L	171 (138; 216)	248 (195; 316)	<0.000001
Thrombocytopenia***, n/%	190/56.7	61/19.0	<0.00001
Lactate dehydrogenase, IU/L	621 (494; 786)	662 (531; 926)	=0.0000007

*Footnotes:** leukocytes<4.0 x10^9/L; ** lymphocytes <1.0 x10^9/L; *** thrombocytes <150.0 x10^9/L

aspartate transaminase (from 47.1 to 65.8 IU/L) and alanine transaminase (from 34.7 to 82.0 IU/L) were seen. There were no other clinically significant adverse events or laboratory abnormalities revealed.

In 42/42 (100%) patients where PRC test AmpliTest SARS-CoV-2 VOC v.2" was applied, mutations L452R and P681R in the S gene were found confirming the presence of the Delta genetic line of SARS-CoV-2.

4. Discussion

In this open-label noncomparative study, we enrolled adult patients admitted to the hospital with moderate COVID-19 and radiologically confirmed pneumonia. Olokizumab was prescribed in accordance with the national guidelines to patients with signs of hyperinflammatory response and/or markers of disease deterioration and poor outcome.

Olokizumab usage in a dose ranging from 64 to 256 mg in one or two injections in addition to standard therapy resulted in a rapid decline in serum CRP, CPK levels, body temperature normalization, and a significant increase in the number of blood leukocytes, lymphocytes, and thrombocytes. It was accompanied by clinical improvement in 69.7% of cases and thus, potentially prevented further ICU admission due to the disease worsening and COVID-19-related deaths.

Our results are consistent with other studies, which have suggested that blockade of IL-6 has a substantial positive effect on patients with severe COVID-19 [6–16]. At the same time, our data support the concept that an early IL-6 blockade can be an effective treatment strategy in moderately ill patients hospitalized with COVID-19. It is worth mentioning that patients were recruited during the high prevalence of the Delta variant of SARS-CoV-2 in Russia, which is characterized by a more severe course with higher hospital admission [17]. The predominance of this genetic line was confirmed by the detection of specific mutations L452R and P681R in the S gene in a subset of the study participants. Interestingly, olokizumab had a favorable safety profile in COVID-19 patients although used in a dose two–four times higher than a standard one recommended for rheumatoid arthritis.

5. Conclusion

This study has several limitations. The number of patients was relatively small and all the patients were recruited in a single clinical center. The open-label and uncontrolled nature of the study mandates caution in the interpretation of the results as such studies are prone to different types of bias. It should be emphasized that all the patients were given standard treatment for COVID-19, including dexamethasone, anticoagulants, and favipiravir. Despite these limitations, the study results have shown that olokizumab appears to affect potential proinflammatory markers and improve the clinical course of moderate COVID-19 in hospitalized adults. An early IL-6 blockade with olokizumab can potentially prevent clinical deterioration in patients with COVID-19 pneumonia, thereby contributing to earlier hospital discharge and better prognosis.

However, there is no doubt that, to confirm our preliminary finding, randomized clinical trials are needed. Before that such clinical questions as which patients would benefit from olokizumab, at what stage of COVID-19, and what dosage regimen is the most appropriate one will remain unanswered.

Declarations

Ethical considerations

This study was approved by the Local Institutional Review Board (records of the meeting from June 7, 2021), and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was not supported by any external sources of funding.

Acknowledgment

The authors express their gratitude to the Hospital for War Veterans №. 3 employees Larin E.S., Kozhevnikova E.V., and Antonova E.V.

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