DOI: 10.26442/00403660.2020.12.200522

Experience of olokizumab use in COVID-19 patients

V.N. Antonov[1,2], G.L. Ignatova[1,2], O.V. Pribytkova[1,2], S.S. Sleptsova[3], E.A. Strebkova[4,5], E.A. Khudyakova[6], A.I. Simakova[7,8], S.Yu. Rabets[9], E.P. Tikhonova[10,11], D.Yu. Kurmaeva[12], M.A. Petrushin[13], A.S. Mashkov[14], E.V. Gayazova[15], I.V. Yasheva[16], M.A. Andreev[17], V.V. Khinovker[18], A.Yu. Karpunin[19], B.V. Berezhanskiy[20]

[1]South Ural State Medical University, Chelyabinsk, Russia;
[2]Regional Clinical Hospital №3, Chelyabinsk, Russia;
[3]Ammosov North-Eastern Federal University, Yakutsk, Russia;
[4]Seredavin Samara Regional Clinical Hospital, Samara, Russia;
[5]Samara State Medical University, Samara, Russia;
[6]St. Luke of Crimea Stary Oskol District Hospital, Belgorod Region, Stary Oskol, Russia;
[7]Pacific State Medical University, Vladivostok, Russia;
[8]Territorial Clinical Hospital №2, Vladivostok, Russia;
[9]Norilsk Inter-District Hospital №1, Norilsk, Russia;
[10]Voyno-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russia;
[11]Karpovich Krasnoyarsk Inter-District Clinical Emergency Hospital, Krasnoyarsk, Russia;
[12]Penza Regional Clinical Tertiary Care Centre, Penza, Russia;
[13]Tver Region Regional Clinical Hospital, Tver, Russia;
[14]Voronovskoye Moscow Clinical Center for Infectious Diseases, Moscow, Russia;
[15]Nizhny Novgorod Region City Clinical Hospital №3 (Nizhny Novgorod Geriatric Center), Nizhny Novgorod, Russia;
[16]Temporary Infectious Diseases Hospital for Coronavirus Disease based at the Cherkess City Clinical Hospital, Cherkessk, Russia;
[17]Republican Tuberculosis Dispensary, Cheboksary, Russia;
[18]Siberian Clinical Research Center, Krasnoyarsk, Russia;
[19]Regional Clinical Hospital, Ryazan, Russia;
[20]R-Pharm JSC, Moscow, Russia

Abstract

Most subjects with the COVID-19 experience mild to moderate symptoms, but approximately 10 % of cases suffer from severe course of disease. IL-6 inhibitors are actively used to neutralize and prevent the "cytokine storm". Olokizumab is a humanized monoclonal antibody belonging to the G4/Kappa immunoglobulin isotype that selectively binds to human IL-6 and effectively neutralizes it.

Aim. To evaluate the efficacy and safety of Artlegia (olokizumab) for the treatment of subjects with a disease caused by the SARS-COV-2 virus in a real-world clinical setting.

Materials and methods. The analysis included data of 610 subjects aged 55.08±12.68 years who received olokizumab at a single dose of 160 mg/mL - 0.4 mL subcutaneously as a preemptive anti-inflammatory therapy. The comparison group included 511 subjects aged 55.23±11.23 years who received standard therapy without IL-6 inhibitors. Control Endpoints: 1. Positive clinical changes on Day 7. 2. Changes in the CRP levels on Days 1, 2, and 7. 3. Duration of oxygen therapy. 4. Number of days in hospital. 5. Number of adverse events. 6. Disease outcome.

Results. If a "cytokine storm" occurs, immune regulatory events will trigger the development of either a protective immune response or an exacerbated inflammatory response. The use of preemptive anti-inflammatory therapy has both a short-term and, most importantly, a long-term effect on the T and B parts of the immune process. These aspects definitely require further research and observation.

Conclusion. The use of olokizumab to treat the new COVID-19 coronavirus disease has demonstrated a positive effect on clinical and laboratory parameters. Primarily, it affects the severity of clinical parameters by improving the general condition already on the first day of observation, and decreasing body temperature to normal values. The changes in the C-reactive protein levels show a significant effect of the IL-6 inhibitor on the systemic inflammatory response.

Keywords: new COVID-19 coronavirus infection, preemptive anti-inflammatory therapy, olokizumab.

For citation: Antonov V.N., Ignatova G.L., Pribytkova O.V., et al. Experience of olokizumab use in COVID-19 patients. Therapeutic Archive. 2020; 92 (12): . DOI: 10.26442/00403660.2020.12.200522

CI — Confidence Interval
ALV — Artificial Lung Ventilation
IL — Interleukin
INF — Interferon
CT — Computed Tomography
CRP — C-Reactive Protein
JIA — Juvenile Idiopathic Arthritis
JAK — Janus Kinase(s) inhibitor(s)
MAS — Macrophage Activation Syndrome

Nowadays, the entire world lives under conditions of a pandemic of the new coronavirus infection COVID-19 that began in late 2019 in the Chinese province of Wuhan [1]. The majority of patients subjects experience mild to moderate symptoms, but approximately in 10 % of cases, they suffer from the severe course of disease [2]. Sepsis, respiratory failure, and acute respiratory distress syndrome are common complications of COVID-19. The risk factors associated with the admission of patients to the intensive care unit and death include old age, comorbidities, increased body mass index, lymphopenia, and increased transaminases, lactate dehydrogenase, D-Dimer, and ferritin [1]. Previously, this was described as cytokine storm syndrome, in which hyperinflammation and multisystemic failure occur as a result of excessive cytokine release due to uncontrolled activation of the immune system [3].

Rheumatologists regularly face these challenges in systemic juvenile idiopathic arthritis (JIA), adult-onset Still's disease, systemic lupus erythematosus, and other systemic diseases. Macrophage activation syndrome (MAS), one of the cytokine storm syndrome forms, develops at least in 10 % of patients with systemic JIA. Compared to patients with systemic JIA without MAS, patients with this complication are more likely to carry heterozygous variants in genes that mediate the release of cytotoxic granules from natural killer (NK) cells and CD8+ T cells; biallelic mutations of these genes cause an inherited form of cytokine storm syndrome termed familial hemophagocytic lymphohistiocytosis (HLH). Decreased cytotoxicity impairs the clearance of infected cells and elimination of activated macrophages, which results in the mass release of proinflammatory mediators. One of these mediators, the interleukin (IL)-6, further impairs the NK cells function. Patients experience a rapid onset of fever, cytopenia, coagulopathy, increased transaminase levels, hyperferritinemia, and multiple organ dysfunction. Historically, the treatment cornerstones were glucocorticoids, intravenous immunoglobulin (IVIG), and cyclosporine. Identification

of key mediators that control MAS, including IL-1β, IL-6, IL-18, and interferon-γ (IFNγ), started a new era of cytokine neutralization, potentially contributing to appreciable decrease in lethality [4].

IL-6 is a pleiotropic cytokine that plays a pivotal role in immune regulation and inflammation [1]. Its importance in understanding both innate and adaptive immune responses is confirmed by a wide range of cells secreting this cytokine, including monocytes, macrophages, T cells, and B cells [5]. IL-6 regulates chemokine-controlled white blood cell transport and induces T cell proliferation and differentiation, as well as antibody production by B cells. IL-6 also promotes the transition from innate to adaptive immunity by regulating activation, differentiation, and proliferation of white blood cells [5]. IL-6 interacts with two receptors, gp80 [also known as IL-6 receptor (IL-6R), CD126] and the signal-transmitting molecule of the gp130 co-receptor (CD130) to form a hexameric signaling complex. The formation of this signaling complex is considered to be a step-by-step process, during which the IL-6 molecule first binds to gp80 to form a dimer, and then to gp130 to form heterotrimers. Two heterotrimers then join to form the final active hexamer signaling complex (gp80: IL-6: gp130). Gp130 is expressed everywhere, while gp80 is present only on certain subpopulations of white blood cells and hepatocytes. Biological therapeutic strategies include inhibition of gp80 IL-6 receptors through the use of tocilizumab or sarilumab, or IL-6 itself in case of using olokizumab [6]. Olokizumab is a humanized monoclonal antibody belonging to the G4/Kappa immunoglobulin isotype. Olokizumab selectively binds to human IL-6 and effectively neutralizes the effects of IL-6 *in vivo* and *in vitro*. Olokizumab was investigated in a series of multi-center international phase III studies, which demonstrated its safety and efficacy in more than 2,400 subjects with rheumatoid arthritis.**Research Program Aim** is to investigate the efficacy and safety of the drug product Artlegia (olokizumab) for the treatment of patients with pathogenic disease caused by the SARS-CoV-2 virus (COVID-19) in a real-world setting.

Acknowledgements:

Ignatova Galina Lvovna, Dr. habil. Med., Professor, Head of Internal Medicine Department at Supplementary Vocational Education Institution, SBHI RCH No. 3 of FSBEI HE SUSMU ORCID: 0000-0002-0877-6554

Pribytkova Olga Vladimirovna, Candidate of Medical Sciences, Head of Clinical Pharmacology Department at SBHI RCH No. 3, sr. external expert, clinical pharmacologist of the Chelyabinsk Government Healthcare Directorate ORCID: 0000-0002-0818-9237

Sleptsova Snezhana Spiridonovna, Dr. habil. Med., Assistant Prof., Head of Infectious Disease, Phthisiology and Dermatovenereology Department at FSAEI HE M. K. Ammosov North-Eastern Federal University ORCID: 0000-0002-0103-4750

Strebkova Elena Alekseevna, Candidate of Medical Sciences, Assistant Prof., Head of Infectious Disease Unit No. 2 SBHI Seredavin SRCH, sr. external expert in HIV-infection diagnostics and treatment issues of the Ministry of Healthcare in Samara region ORCID: 0000-0002-0854-2264

Khudyakova Elena Alekseevna, Head of Infectious Disease Unit at RSBHI Stary Oskol District Hospital of St. Luke of Crimea ORCID: 0000-0002-4408-1581

Simakova Anna Ivanovna, Dr. habil. Med, Assistant Prof., Head of Infectious Disease Department at SBHI DCH No. 2 of the FSBEI HE TSMU, sr. external expert in infectious diseases in Primorsky Krai ORCID: 0000-0002-3334-4673

Rabets Stanislav Yurievich, Deputy Chief Medical Officer for Organization and Methodological Support, clinical pharmacologist, RSBHI NIDH No. 1 ORCID: 0000-0003-4853-4127

Tikhonova Elena Petrovna, Dr. habit. Med., Professor, Head of Infectious Disease and Epidemiology Department with VE training course, FSBEI HE Prof. V. F. Voino-Yasenetsky KSMU, RSBHI N. S. Karpovich Krasnoyarsk Inter-District Clinical Emergency Hospital ORCID: 0000-0001-6466-9609

Kurmaeva Jamilya Yusupovna, Candidate of Medical Sciences, Deputy Chief Medical Officer for Medicine, SBHI Penza Regional Clinical Tertiary Care Centre ORCID: 0000-0001-7989-7647

Petrushin Maksim Aleksandrovich, Head of Anaesthesiology and Reanimation Unit at SBHI RCH No. 3 ORCID: 0000-0002-2780-5138

Mashkov Aleksandr Sergeevich, Head of 6th Infectious Disease Unit at Voronovskoe Moscow Clinical Center for Infectious Diseases ORCID: 0000-0003-3465-8372

Gayazova Elena Vladimirovna, neurologist, SBHI Nizhny Novgorod Region City Clinical Hospital No. 3 ORCID: 0000-0001-9621-3550

Yasheva Inna Vladimirovna, Head of Pulmonary Department at Temporary Infectious Diseases Hospital for Coronavirus Disease based at the RSBHI Cherkess City Clinical Hospital, Karachay-Cherkess Republic ORCID: 0000-0002-2228-5137

Andreev Mikhail Anatolievich, Deputy Chief Medical Officer for Medicine at BI Republican Tuberculosis Dispensary ORCID: 0000-0002-4548-2598

Kinovker Vladimir Vladimirovich, Candidate of Medical Sciences, Head of Anaesthesiology and Reanimation Unit at FSBI Federal Siberian Clinical Research Center ORCID: 0000-0002-3162-6298

Karpunin Andrey Yurievich, Candidate of Medical Sciences, Chief Medical Officer at SBI Ryazan Region Regional Clinical Hospital ORCID: 0000-0003-0837-8895

Berezhansky Boris Vitalievich, Candidate of Medical Sciences, Sr. Med. Advisor, R-Pharm JSC. ORCID: 0000-0002-2551-9584

Materials and Methods

We have performed a retrospective analysis of data collected in routine clinical practice during hospitalization of patients with new coronavirus infection caused by the SARS-CoV-2 virus (COVID-19) from May 31, 2020 until August 31, 2020 at 19 clinical centers of the Russian Federation. The Protocol included data from 610 patients who received a preemptive anti-inflammatory therapy with Artlegia (olokizumab), solution for subcutaneous administration, 160 mg/ml – 0.4 ml, and standard therapy according to the criteria of the interim guidelines "Prevention, Diagnosis and Treatment of the New Coronavirus Disease (COVID-19)" of the RF MoH, Version 7.

Inclusion criteria:

1. Subject age: ≥18,
2. Confirmed diagnosis of COVID-19,
3. Thoracic MSCT (CT1–3) or changes in thoracic radiograms ranging from 0 to 75 % in combination with 2 or more criteria:
   - hyperthermia ≥ 38 °C
   - oxygen therapy
   - C-reactive protein ≥ 30 mg/L

The control group included 511 subjects with confirmed COVID-19 diagnosis, who were prescribed standard therapy, according to the interim guidelines "Prevention, Diagnosis and Treatment of the New Coronavirus Disease (COVID-19)" of the RF MoH, Version 7, without preemptive anti-inflammatory therapy with IL-6 or Janus kinase (JAK) inhibitors. Analysis involved the following data obtained from inpatient medical records: age, gender, race, date of hospitalization, department, extent of pulmonary involvement as criteria for the severity of a subject's condition, the day of Artlegia administration after the first signs of coronavirus disease and after hospitalization, body temperature on the day of Artlegia administration (Day 0) and on Days 1, 2, 7 after the drug administration, CRP changes on Days 1, 2, 7 compared to the day of administration (Day 0), administration of other immunosuppressive drugs used for COVID-19 treatment during this hospitalization, the need and duration of oxygen therapy and artificial lung ventilation, the duration of treatment at the intensive care unit (ICU), hospitalization duration, the development of adverse events and the disease outcome.

Control Endpoints of the Research Program:

1. Positive clinical changes on Day 7 defined as the number and proportion of subjects with decrease in body temperature and CRP levels on Day 7 or the previous day, if no records were made on Day 7.

Contact Information:
Vladimir Nikolayevich Antonov, Dr. habit. Med., Professor at Internal Medicine Department at Supplementary Vocational Education Institution, SBHI RCH No. 3 of FSBEI HE SUSMU Tel: +7(351)742-66-40; e-mail: ant-vn@yandex.ru; ORCID: 0000-0002-3531-3491

Table 1. **Main Subject Demographics**

Parameter	Olokizumab Treatment Group Subjects (*n*=610)	Control Group Subjects (*n*=511)
	Age	
n	610	511
M	55.08	55.23
CI <95%	54.07-56.08	53.34-57.11
	Sex, abs. (%)	
Female	286 (46.89)	234 (45.8)
Male	324 (53.11)	277 (54.2)
	Race, abs. (%)	
Asian	71 (11.64)	64 (12.5)
Caucasian	539 (88.36)	447 (87.5)
	Hospitalization (%)	
General medicine unit	525 (86.07)	508 (99.4)
ICU	85 (13.93)	5 (0.6)
	Changes in MSCT at the time of hospitalization, abs. (%)	
CT-1	43 (7)	24 (4.7)
CT-2	316 (51.8)	357 (69.9)
CT-3	251 (41.2)	130 (25.4)
Duration of O2 therapy	8.33 (CI 95 %, 7.88–8.77)	9.07 (CI 95 %, 8.56–9.46)
Hospitalization days, total	17.68 (CI 95 %, 17.17–18.18)	19.04 (CI 95 %, 18.21–19.87)*
Hospitalization days after the preemptive anti-inflammatory therapy	14.31 (CI 95 %, 13.83- 14.80)	15.74 (CI 95 %, 15.12–16.35)*
Number of adverse events (%)	15 (2.46)	23 (4.5)
	Disease outcome (%)	
Recovery	596 (97.7)	490 (95.9)
Death	14 (2.3)	21 (4.1)

*p <0.05

2. Changes in the CRP levels on therapy days 1, 2, and 7.
3. Duration of oxygen therapy.
4. Hospitalization days.
5. Number of adverse events.
6. Disease outcome.

If any data to be collected within this program was unavailable, it was considered missing. Since the program analyzed the changes in a subject's condition, the included subjects could not have missing data on the day of Artlegia administration, even if there were data for all the subsequent days.

All the data were analyzed using descriptive statistics methods both in overall group of subjects and in certain subgroups. Descriptive statistics for quantitative variables included the mean, the standard deviation (SD), the median, the first and third quartiles, the minimum and maximum values, and the number of valid observations (N). The qualitative parameters are presented as frequencies and percentages; 95 % confidence intervals (CI) around the point estimate are also provided (where applicable). Statistical significance of the intergroup differences in qualitative (categorical) parameters was evaluated using a Fisher's exact test or chi-square test ($\chi 2$ test), whereas the quantitative data were evaluated with a Kruskal-Wallis test and Dunn's test for intergroup comparisons.

Results

The demographic characteristics of subjects are summarized in **Table 1**.

Main clinical characteristics of the subjects are presented in **Table 2**.

Analysis of the changes in body temperature decrease has shown the following results: in the subgroup of preemptive anti-inflammatory therapy with olokizumab, 92.1 % (n=562) of the subjects had a decrease to normal or subfebrile values on Day 1. By the 7th day of observation, this parameter showed stable positive trends in 590 subjects (96.7 %). In the subgroup of subjects who received standard therapy without the use of IL-6 inhibitors, the body temperature by the 7th day of observation normalized only in 61.8 % of cases.

The changes in the C-reactive protein levels during the use of olokizumab showed a pronounced trend towards its decrease in 89.8 % of cases versus 21.9 % subjects on standard therapy. This difference was statistically significant.

Positive clinical trends on Day 7 (or the previous day) after administration of Artlegia were registered for 592 (97.21 %) subjects **(Table 3)**. Among subjects with CT-1, CT-2, or CT-3, the number of people with positive clinical trends on Day 7 (or the previous day) after administration of Artlegia was 40 (95.24 %), 308 (97.47 %) and 244 (97.21 %).

Table 2. **Changes in Main Clinical Characteristics of Subjects by the 7th Day of Observation**

Parameter of Interest	Olokizumab Treatment Group Subjects (*n*=610), abs. (%)		Control Group Subjects (*n* = 511), abs. (%)		Reliability, p
	Day 1	Day 7	Day 1	Day 7	
Body temperature decrease	562 (92.1)	590 (96.7)	84 (16.4)	316 (61.8)	<0.05
CRP level decrease	441 (72.3)	548 (89.8)	67 (13.1)	112 (21.9)	<0.05

Table 3. **Positive clinical trends on Day 7 (total and according to CT scans)**

Group	CT-1	CT-2	CT-3	Total	Reliability
Olokizumab Treatment Group Subjects (*n*=610)	40 (95.24%)	308 (97.47%)	244 (97.21%)	592 (97.21%)	0.632 (f)
Control Group Subjects (*n*=511)	11 (45.8%)	134 (37.5%)	87 (66.9%)	232 (45.4%)	0.411 (f)
Reliability	0.002 (f)*	0.001 (f)*	0.002 (f)*	0.002 (f)*	

Note: * (f) is the Fisher's ratio test

Table 4. **Duration of Hospitalization after Administration of Olokizumab (total and according to CT-scans)**

Parameter	CT-1	CT-2	CT-3	Total	Comparison
n	43	316	251	610	
M	11.88	13.53	15.71	14.31	
SD	4.02	5.40	6.93	6.12	
CI 95%	10.65–13.12	12.93–14.13	14.85–16.57	13.83–14.80	<0.001(kw)*
Min–Max	7.00–25.00	2.00–36.00	3.00-53.00	2.00-53.00	
Me	11.00	13.00	15.00	13.00	
Q1–Q3	9.00–13.00	10.00-17.00	11.00-19.00	10.00-17.00	

Note: *(kw) is the Kruskal-Wallis test

There was no statistically significant difference in the frequency of positive trends in subjects with CT-1, CT-2 or CT-3 (p = 0.632). The control group subjects showed less pronounced positive trends, presented in Table 3, with significant statistical differences versus the group treated with olokizumab.

The average duration of stay in hospital after administration of Artlegia was 14.31 ± 6.12 (2 to 53) days **(Table 4)**; in subjects with CT-1 (*n* = 43), CT-2 (*n* = 316) or CT-3 (*n* = 251), this parameter reached 11.88 ± 4.02 (7 to 25), 13.53 ± 5.40 (2 to 36) and 15.71 ± 6.93 (3 to 53) days, respectively ($p < 0.001$).

In the subjects with CT-1 who received no adjunctive therapy (*n* = 10) or received corticosteroids (*n* = 32), the average duration of stay in hospital after administration of Artlegia was 14 ± 3.94 (7 to 20) and 10.81 ± 3.04 (7 to 19) days, respectively ($p = 0.014$). In the subjects with CT-2 who received no adjunctive therapy (*n* = 39), who received corticosteroids (*n* = 265) or corticosteroids and JAK inhibitors (*n* = 11), the average duration of stay in hospital after administration of Artlegia was 11.72 ± 3.77 (2 to 21), 13.45 ± 5.25 (5 to 36) and 21.64 ± 7.27 (13 to 34) days, respectively ($p < 0.001$). In the subjects with CT-3 who received no adjunctive therapy (*n* = 10), who received corticosteroids (*n* = 234) or corticosteroids and JAK inhibitors (*n* = 7), the average duration of stay in hospital after administration of Artlegia was 12.10 ± 5.78 (3 to 20), 15.61 ± 6.65 (7 to 53) and 24.43 ± 10.95 (13 to 39) days, respectively ($p = 0.014$).

The duration of oxygen therapy after administration of Artlegia in the research population (*n* = 586) was 8.33 ± 5.48 (from 1 to 35) days. Subgroup analysis in subjects with CT-1 (*n* = 38), CT-2 (*n* = 303), or CT-3 (*n* = 245) showed that the mean duration of oxygen therapy after administration of Artlegia was 6.42 ± 4.16 (1 to 22), 7.59 ± 4.74 (1 to 32), and 9.53 ± 6.24 (1 to 35) days. The differences in the oxygen therapy duration after the use of Artlegia in the groups formed by CT findings were statistically significant ($p < 0.001$; see **Table 5**). The duration of oxygen therapy after administration of Artlegia in subjects treated with corticosteroids and JAK inhibitors was significantly higher than in subjects treated with corticosteroids or in subjects who received no adjunctive therapy ($p < 0.001$ in both cases). Oxygen therapy in the control group lasted 9.07 ± 6.21 days without statistically significant differences; the group treated with Artlegia had similar parameters.

Adverse events in the group exposed to Artlegia were registered in 15 (2.46 %) subjects, each of whom received adjunctive corticosteroid therapy; 11 (3.50 %) of them had AEs before the use of Artlegia.

Table 5. **Duration of Oxygen Therapy after Administration of Olokizumab (total and according to CT-scans)**

Parameter	CT-1	CT-2	CT-3	Total	Comparison
n	38	303	245	586	
M	6.42	7.59	9.53	8.33	
SD	4.16	4.74	6.24	5.48	
CI 95%	5.05-7.79	7.06-8.13	8.74-10.31	7.88-8.77	<0.001(kw)*
Min–Max	1.00-22.00	1.00-32.00	1.00-35.00	1.00-35.00	
Me	5.50	6.00	8.00	7.00	
Q1–Q3	4.00–7.00	5.00-10.00	5.00-13.00	5.00-10.00	

Note: *(kw) is the Kruskal-Wallis test

Table 6. **Lethal Outcome Rate (total and according to CT-scans)**

Parameter	CT-1	CT-2	CT-3	Total	Comparison
Yes	1 (2.33%)	1 (0.32%)	12 (4.78%)	14 (2.30%)	< 0.001 (f)*
No	42 (97.67%)	315 (99.68%)	239 (95.22%)	596 (97.70%)	

Note: * (f) is the Fisher's ratio test

In the research population, 14 (2.30 %) deaths occurred in 14 (2.64 %) subjects treated with corticosteroids: of them, 13 (1 patient with CT-1, 1 patient with CT-2, and 11 subjects with CT-3) were on lung ventilators, while 1 subject (with CT-3) was not mechanically ventilated. Thus, the vast majority of deaths were registered in subjects who received mechanical ventilation, which confirms the relationship between the occurrence of deaths and the severity of subjects' condition, but not the therapy being conducted. In 1 case (0.16 %), a decrease in the number of white blood cells was registered.

During the study, deaths were registered in 14 (2.30 %) subjects, of which 1 (2.33 %) had CT-1, 1 (0.32 %) — CT-2, and 12 (4.78 %) had CT-3. The differences in the lethal outcome rate in the groups formed by CT findings were statistically significant ($p < 0.001$; see **Table 6**).

In subjects with CT-1, there was 1 death (2.38 %) that occurred in 1 (3.12 %) subject treated with corticosteroids. In subjects with CT-2, there was also 1 death (0.32 %) that occurred in 1 (0.38 %) subject treated with corticosteroids. In subjects with CT-3, there were 12 deaths (4.78 %) that also occurred in 12 (5.13 %) subjects treated with corticosteroids. There were no statistically significant intergroup differences ($p = 1.00$). At the same time, the subjects in the olokizumab group had a more severe course of disease at baseline.

Discussion

The latest publications on the evaluation of inflammatory responses of lung tissue to the effects of the new coronavirus strongly suggest that SARS-CoV-2 differs from other coronaviruses in its ability to replicate in lung tissue, evade the antiviral effects of INF-I and INF-III, activate innate responses and induce the production of cytokines necessary for the recruitment of adaptive immunity cells [1]. The transition between innate and adaptive immune responses is crucial for the clinical progress of SARS-CoV-2 disease. It is at this critical moment that immune regulatory events that are still poorly understood will trigger the development of either a protective immune response or an exacerbation of the inflammatory response [7, 8]. A protective response depends on T cells, with CD4 helping B cells to produce specific neutralizing antibodies and CD8 cytotoxic cells that can eliminate infected cells. It is should be noted that 80 % of COVID-19 infiltrating cells are CD8 [9]. On the contrary, a dysfunctional response that is unable to suppress virus replication and eliminate infected cells can lead to an exacerbation of the inflammatory response that can cause a cytokine storm clinically manifested by severe acute respiratory distress syndrome (ARDS) and systemic consequences such as disseminated intravascular coagulation. The primate model of SARS-CoV infection showed that the virus replicated in the lungs for up to 10 days after infection; but, oddly enough, lung inflammation was more intense after the virus was eliminated, peaking on Day 14 and remaining so until Day 28. These results suggest that an early phase dependent on viral replication does occur, while a later viral-independent, immune-dependent phase seems to be accompanied by an exacerbated inflammatory component. The virus-independent phase was explained by an inflammatory reaction secondary to ACE2 inhibition, or an autoimmune phenomenon due to the epitope spreading caused by prolonged tissue destruction [10, 11].

The use of preemptive anti-inflammatory therapy exerts an impact on both parts of the immune process having both a short-term and, most importantly, a long-term effect. These aspects undoubtedly require further research and observation.

Findings. The use of olokizumab for treatment of the new coronavirus infection COVID-19 has demonstrated a positive effect on clinical and laboratory parameters. First of all, it affects the severity of clinical parameters by improving the general condition already on the first day of observation, and decreasing body temperature to normal values. The changes in the CRP levels show a significant effect of the IL-6 inhibitor on the systemic inflammatory response.

Conclusion

The first results of the Research Program for pragmatic study of the Artlegia (olokizumab) drug efficacy and safety in the treatment of patients with pathogenic disease caused by SARS-CoV-2 virus (COVID-19) have demonstrated the possibility to control one of the main pathogenic components in COVID-19 development, i. e. inflammation. Clinical and laboratory efficacy of the drug has been demonstrated. The results obtained give rise to further scientific inquiry and arrangement of long-term and more extensive clinical studies.

Collision of Interests

Berezhansky B. V. is an employee of the R-Pharm JSC.

REFERENCES

1. Garrfa LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Front Immunol.* 2020;11:1441. doi: 10.3389/fimmu.2020.01441
2. Pascarella G, Strumia A, Piliego Ch, et al. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med*. 2020;288(2):192-206. doi: 10.1111/joim.13091
3. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 Cytokine Storm; What We Know So Far. *Front Immunol*. 2020;11:1446. doi: 10.3389/fimmu.2020.01446.
4. Mahmudpour M, Roozbeh J, Keshavarz M, et al. *Cytokine*. 2020;133:155151. doi: 10.1016/j.cyto.2020.155151
5. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75:1564-81. doi: 10.1111/all.14364
6. Shaw S, Bourne T, Meier C, et al. Discovery and characterization of olokizumab: a humanized antibody targeting interleukin-6 and neutralizing gp130-signaling. *MAbs.* 2014;6(3):774-82. doi: 10.4161/mabs.28612; https://pubmed.ncbi.nlm.nih.gov/24670876
7. Manjili RH, Zarei M, Habibi M, Manjili MH. COVID-19 as an acute inflammatory disease. *J Immunol*. 2020;205:12-9. doi: 10.4049/jimmunol.2000413
8. Felsenstein S, Herbert AJ, McNamara SP, Hedrich CM. COVID-19: Immunology and treatment options. *Clin Immunol.* 2020;215:108448. doi: 10.1016/j.clim.2020.108448.
9. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. *J Med Virol.* 2020;92:424-32. doi: 10.1002/jmv.25685
10. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol.* 2005;5:917-27. doi: 10.1038/nri1732
11. Huang AT, Garcia-Carreras B, Hitchings TDM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. *Nat Commun*. 2020;11(1):4704. doi: 10.1038/s41467-020-18450-4

Received on 11/20/2020.