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CHARACTERISTICS OF OLOKIZUMAB PHARMACOKINETICS IN PATIENTS WITH NOVEL CORONAVIRUS INFECTION COVID-19

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The aim of the article is to study pharmacokinetic characteristics of intravenous olokizumab in patients with moderate COVID-19 to relieve a hyperinflammation syndrome.

Materials and methods. The pharmacokinetic study was conducted as a part of a phase III clinical study (RESET, NCT05187793) on the efficacy and safety of a new olokizumab regimen (intravenous, at the doses of 128 mg or 256 mg) in COVID-19 patients. Plasma concentrations of olokizumab were determined by the enzyme immunoassay. The population analysis was performed using a previously developed pharmacokinetic model based on a linear two compartment.

Results. The pharmacokinetic analysis included the data from 8 moderate COVID-19 patients who had been administrated with olokizumab intravenously at the dose of 128 mg. According to the analysis results in this population, there was an increase in the drug clearance, compared with the data obtained in healthy volunteers and the patients with rheumatoid arthritis: 0.435, 0.178 and 0.147 l/day, respectively. The parameters analysis within the framework of a population pharmacokinetic model showed that the main factors for the increased olokizumab clearance are a high body mass index. In addition, the presence of COVID-19 itself is an independent factor in increasing the drug clearance.

Conclusion. After the intravenous olokizumab administration, an increase in the drug clearance is observed in moderate COVID-19 patients against the background of the disease course. The main contribution to the increased clearance is made by the characteristics of the population of COVID-19 patients associated with the risk of a severe disease and inflammation. When administered intravenously at the dose of 128 mg, a therapeutically significant olokizumab level was maintained throughout the acute disease phase for 28 days.

Keywords: COVID-19, olokizumab; clearance; pharmacokinetic model

Abbreviations: IL(s) – interleukins; PAIT – proactive anti-inflammatory therapy; Ig(s) – immunoglobulins; PK – pharmacokinetics; RA – rheumatoid arthritis; RESET – hyperinflammation; CRP – C-reactive protein; CT – computer tomography; RR – respiratory rate; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ULN – upper limit of normal; BMI – body mass index; ELISA – enzyme-linked immunosorbent assay; $T_{1/2}$ – half-life; AUC_{0-t} – area under the concentration-time pharmacokinetic curve from zero to the last blood draw; Kel – elimination constant; $AUC_{0-\infty}$ – area under the concentration-time curve from time zero to infinity; CL – clearance; T_{max} – time to reach the maximum concentration of olokizumab in blood plasma; C_{max} – maximum concentration of olokizumab in blood plasma; MRT – Mean Resident Time.

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ОСОБЕННОСТИ ФАРМАКОКИНЕТИКИ ОЛОКИЗУМАБА У ПАЦИЕНТОВ С НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ COVID-19

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Цель. Изучение особенностей фармакокинетики олокизумаба при внутривенном введении у пациентов с COVID-19 среднетяжелого течения для купирования синдрома гипервоспаления.

Материалы и методы. Изучение фармакокинетики проводилось в рамках клинического исследования III фазы (исследование RESET, NCT05187793) эффективности и безопасности нового режима применения олокизумаба (внутривенно, в дозах 128 мг или 256 мг) у пациентов с COVID-19. Определение концентрации олокизумаба в плазме крови проводили методом иммуноферментного анализа. Популяционный анализ выполнен с помощью ранее разработанной фармакокинетической модели на основе линейной двухкамерной модели.

Результаты. В анализ фармакокинетики были включены данные 8 пациентов с COVID-19 среднетяжелого течения, получавшие олокизумаб в дозе 128 мг внутривенно. Согласно результатам анализа в данной популяции наблюдалось увеличение клиренса препарата, по сравнению с данными, полученными у здоровых добровольцев и пациентов с ревматоидным артритом: 0,435, 0,178 и 0,147 л/сут, соответственно. Анализ параметров в рамках популяционной фармакокинетической модели показал, что основными факторами повышенного клиренса олокизумаба являются высокий индекс массы тела. Кроме того, независимым фактором повышения клиренса препарата является само наличие COVID-19.

Заключение. У пациентов со среднетяжелым течением COVID-19 после внутривенного введения олокизумаба наблюдается увеличение клиренса препарата на фоне течения заболевания. Основной вклад в повышенный клиренс вносят особенности популяции пациентов с COVID-19, связанные с риском тяжелого течения заболевания и выраженным воспалением. При внутривенном введении в дозе 128 мг терапевтически значимый уровень олокизумаба сохранялся в течение всей острой фазы заболевания на протяжении 28 дней.

Ключевые слова: COVID-19; олокизумаб; клиренс; фармакокинетическая модель

Список сокращений: ИЛ – интерлейкины; УПТ – упреждающая противовоспалительная терапия; Ig – иммуноглобулины; ФК – фармакокинетика; РА – ревматоидный артрит; RESET – гипервоспаление; СРБ – С-реактивный белок; КТ – компьютерная томография; ЧДД – частота дыхательных движений; АЛТ – аланинаминотрасфераза; АСТ – аспартатаминотрансфераза; ВГН – верхняя граница нормы; ИМТ – индекс массы тела; ИФА – иммуноферментный анализ; $T_{1/2}$ – период полувыведения; AUC_{0-t} – площадь под фармакокинетической кривой «концентрация-время» от нуля до последнего отбора крови; K_{el} – константа элиминации; $AUC_{0-\infty}$ – площадь под фармакокинетической кривой «концентрация-время», начиная с нулевого значения времени, экстраполированная до бесконечности; CL – клиренс; T_{max} – время достижения максимальной концентрации олокизумаба в плазме крови; C_{max} – максимальная концентрация олокизумаба в плазме крови; MRT – среднее резидентное время.

INTRODUCTION

In December 2019, a large outbreak of a disease caused by a novel coronavirus (SARS-CoV-2) affecting the lower respiratory tract, occurred in Wuhan, China [1].

Most patients suffer from a mild form of the disease (like an acute respiratory viral infection), but the infection can turn into an acute respiratory distress syndrome. In this case, there is a rapid replication of the virus, a rapid release of pro-inflammatory cytokines against the background of the inflammatory infiltrates formation in the lung parenchyma and pulmonary vascular endothelium, damage to the alveoli, vascular microthrombosis, etc. There is a pattern of systemic hyperinflammation with increased levels of interleukins (ILs) cytokines such as IL-1β, IL-1Ra, IL-6 and the IL-2

receptor. The progressive development of systemic pathological inflammation results in a pronounced increase in the severity of the disease and the development of multiorgan damage [2–4].

According to the Interim Guidelines (IGs) of the Russian Ministry of Health "Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19)"[1], the use of proactive anti-inflammatory therapy (PAIT) in combination with active anticoagulant therapy is currently the standard of care. Monoclonal antibodies – blockers of the IL-6, IL-6, IL-1 receptors, can be used among others as PAIT.

Olokizumab (Artlegia®) is a humanized monoclonal antibody of the immunoglobulin (Ig) G4/kappa isotype that can specifically bind to the IL-6 molecule. 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 [5–7]. 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, 9].

Olokizumab was originally developed as a drug for the treatment of rheumatoid arthritis (RA) and has successfully passed a full-fledged clinical development program that included phase II studies [10] in 380 patients, and phase III studies in 2443 patients (CREDO 1[2] , CREDO 2[3], CREDO 3[4] and CREDO 4[5]), as well as post-marketing studies [11]. According to the studies, the recommended olokizumab dose in RA is 64 mg once every 2 or 4 weeks when administered subcutaneously. In case of pathogenetic therapy of a cytokine release syndrome in a new coronavirus infection (COVID-19) – 64 mg subcutaneously once.

Subsequently, the effect of olokizumab was studied in COVID-19 patients. The use of olokizumab as a part of the complex therapy for COVID-19 revealed a number of pharmacokinetic characteristics of the drug in this population, compared with healthy volunteers and RA patients. In general, the patient population in which olokizumab was prescribed as proactive anti-inflammatory therapy (PAIT) is characterized by a number of trends in both demographic data and laboratory parameters. In particular, a body mass index, or rather overweight, which, in turn, is a risk factor for severe COVID-19, has a known effect on the pharmacokinetics of drugs. In COVID-19, a typical pattern of deviations in the biochemical analysis of blood is observed: an increase in the levels of inflammatory markers, a change in the levels of protein fractions, reflecting the course and severity of the inflammatory process, which also affects the drugs pharmacokinetics.

THE AIM of the article is to study pharmacokinetic characteristics of intravenous olokizumab in patients with moderate COVID-19 to relieve hyperinflammation syndrome.

MATERIALS AND METHODS

Study design

Currently, according to the Interim guidelines (version 16 dated 18 Aug 2022), the intravenous administration of olokizumab is included in the recommended standards of COVID-19 therapy. The pharmacokinetics of the drug when administered intravenously in COVID-19 patients, was evaluated as a part of a multicenter, open, randomized phase III research, the aim of which was to study the efficacy and safety of a new olokizumab regimen (at the doses of 128 and 256 mg, respectively, administered intravenously) in COVID-19 patients with signs of hyperinflammation (RESET). The randomization of patients in the study was central and it was performed using an electronic system. The patients were randomized into 2 groups at the ratio of 1:1 – the olokizumab group (group 1) and the comparison group (group 2). In order to evenly distribute patients into the treatment groups, the stratification was carried out according to the following criteria:

- according to the need for the oxygen support at screening (yes / no),
- the presence of a concomitant disease that is a risk factor for severe COVID-19 (no risk factors or there is one or more risk factors).

Thus, as a result of the stratification, the patients in groups will be equivalent in terms of the presence of respiratory failure and risk factors for severe COVID-19.

Selection criteria for the study

The RESET study was conducted with the approval

[1] Interim Guidelines of the Russian Ministry of Health "Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19), version 16, 18.08.2022. Available from: https://static-0.minzdrav.gov.ru

[2] Evaluation of the Effectiveness and Safety of Two Dosing Regimens of Olokizumab (OKZ), Compared to Placebo, in Subjects With Rheumatoid Arthritis (RA) Who Are Taking Methotrexate But Have Active Disease (CREDO 1). Available from: https://grlsbase.ru/clinicaltrails/clintrail/2763

[3] Evaluation of the Efficacy and Safety of Two Dosing Regimens of Olokizumab (OKZ), Compared to Placebo and Adalimumab, in Subjects With Rheumatoid Arthritis (RA) Who Are Taking Methotrexate But Have Active Disease (CREDO 2). Available from: https://clinicaltrials.gov/ct2/show/NCT02760407

[4] Evaluation of the Efficacy and Safety of Two Dosing Regimens of Olokizumab (OKZ), Compared to Placebo, in Subjects With Rheumatoid Arthritis (RA) Who Were Taking an Existing Medication Called a Tumour Necrosis Factor Alpha Inhibitor But Had Active Disease (CREDO 3). Available from: https://clinicaltrials.gov/ct2/show/NCT02760433

[5] Efficacy and Safety of Olokizumab in Subjects With Moderately to Severely Active Rheumatoid Arthritis (CREDO 4). Available from: https://clinicaltrials.gov/ct2/show/NCT03120949

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of the Ethics Council of the Department for Regulation of the Circulation of Medicines (Ministry of Health of the Russian Federation, Protocol No. 273 dated 20 Apr 2021); the local ethics committees of Voronezh Regional Clinical Hospital No. 1 (Protocol No. 117 dated 22 Jul 2021) and Inozemtsev City Clinical Hospital (Protocol No. 11 dated 28 May 2021). The results of the pharmacokinetic study in the subgroup of COVID-19 patients, compared with the data from the previous studies in healthy volunteers and RA patients, are presented in this paper. The study included hospitalized patients with a confirmed moderate-to-severe coronavirus infection and signs of hyperinflammation, aged over 18 years.

The main inclusion criteria were: moderate COVID-19, pneumonia on computer tomography (CT) and the body temperature > 38°C, in combination with 1 or more features, including the saturation level (SpO_2) < 95%, respiratory rate (RR) > 22, dyspnea on exertion, C-reactive protein (CRP) >10 mg/l; the presence of one of the risk factors (diabetes mellitus, severe cardiovascular pathology, chronic renal failure, oncological pathology, obesity, or age ≥65 years); the presence of the hyperinflammation signs (a body temperature ≥38°C for 2 days or more, in combination with 1 or more signs: a CRP level >3×upper limit of normal (ULN), the leukocyte count – 2.0–3.5 × 10^9/l, the absolute number of lymphocytes – 1.0–1.5×10^9/l).

The main exclusion criteria were: a severe or extremely severe COVID-19 course, the presence of severe laboratory abnormalities (hemoglobin <80 g/l, an absolute neutrophil count <0.5×109/l, a leukocyte count <2.0×109/l, a number of platelets <50 x 109/L, alanine aminotransferase (ALT) ≥ 3.0 × ULN and/or aspartate aminotransferase (AST) ≥ 3.0 × ULN), the creatinine clearance < 30 ml/min, confirmed sepsis by pathogens other than COVID- 19, a high probability of a disease progression to death within the next 24 hours.

Selection criteria for the pharmacokinetics subgroup

The pharmacokinetics (PK) study subgroup included patients with a body mass index (BMI) in the range of 18.5–35.0 kg/m^2 who had signed an additional voluntary informed consent form for the inclusion in the PK study. A total of 9 patients were included in the PK subgroup. These patients were administrated with Artlegia® (INN: olokizumab), a solution for the subcutaneous administration, 160 mg/mg, as an intravenous 60-minute infusion, at the dose of 128 mg (8 patients were administrated with the drug once at the dose of 128 mg), 1 patient was not included into statistical analysis (total dose 256 mg). 1 patient was administrated with the drug twice with a total dose of 256 mg).

In addition to olokizumab, the patients received baricitinib (4 mg/day, for 7 days) and low-doses of glucocorticosteroids (dexamethasone at the doses of 4–20 mg/day IV or IM, or methylprednisolone at the dose of 1 mg/kg intravenously every 12 hours), as well as etiotropic therapy for COVID-19 (favipiravir or remdesivir), symptomatic and anticoagulant therapy drugs.

In the patients included in the PK assessment subgroup, blood biosamples were taken to study olokizumab concentrations as follows: before the start of the infusion, then after 2, 4, 8, 24, 48 and 72 hours; then every day, starting from 4 to 10 days; at the end on days 14 and 28 after the first administration of the drug (i.e. from the moment the infusion began). After the selection, plasma biosamples were frozen and stored at the temperature not exceeding –65°C.

For the analysis of biosamples, a bioanalytical method based on enzyme immunoassay (ELISA) was developed. The method is based on the interaction of olokizumab with IL-6 associated with goat antibodies to human IL-6 immobilized on the surface of the plate. The method was validated in the concentration range of 2.5–100 μg/ml.

Statistical analysis

To assess a possible influence of various factors on the olokizumab clearance, the results were combined with a previously created phases 1 and 2 database of olokizumab clinical trials, including the data from the pharmacokinetic samples analysis of 30 healthy volunteers and 30 RA patients, and the ones who had received a single intravenous olokizumab injection at various concentrations [12].

The description of the olokizumab pharmacokinetics was performed using a linear 2 compartment model with the absorption kinetics and the first order elimination. The model parameterization included pharmacokinetic parameters such as clearance (CL), an distribution volume (V), an elimination rate constant (K_{el}) and rate constants of exchange between compartments (Q/Vc, Q/Vp) (Fig. 1). Interindividual variability (IIV) parameters were included in the final model for the volume of distribution parameters of the central (Vc) and peripheral compartments (Vp). The influence of the following covariates was assessed: age, sex, body weight, serum albumin, liver enzymes, bilirubin, creatinine clearance. Since study CL04041094 did not collect data on participants' albumin levels, for modeling purposes, missing individual albumin levels were reconstructed using the following formula (ALB = –0.4714×CRP+50.714) based on the literature data [13].

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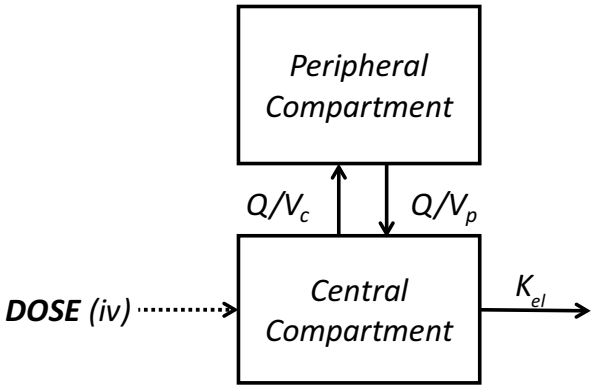

Figure 1 – Diagram of linear two compartment model to describe olokizumab pharmacokinetics
Note: Q/Vc, Q/Vp – speed constants of exchange between cameras; K_{el} – elimination rate constant.

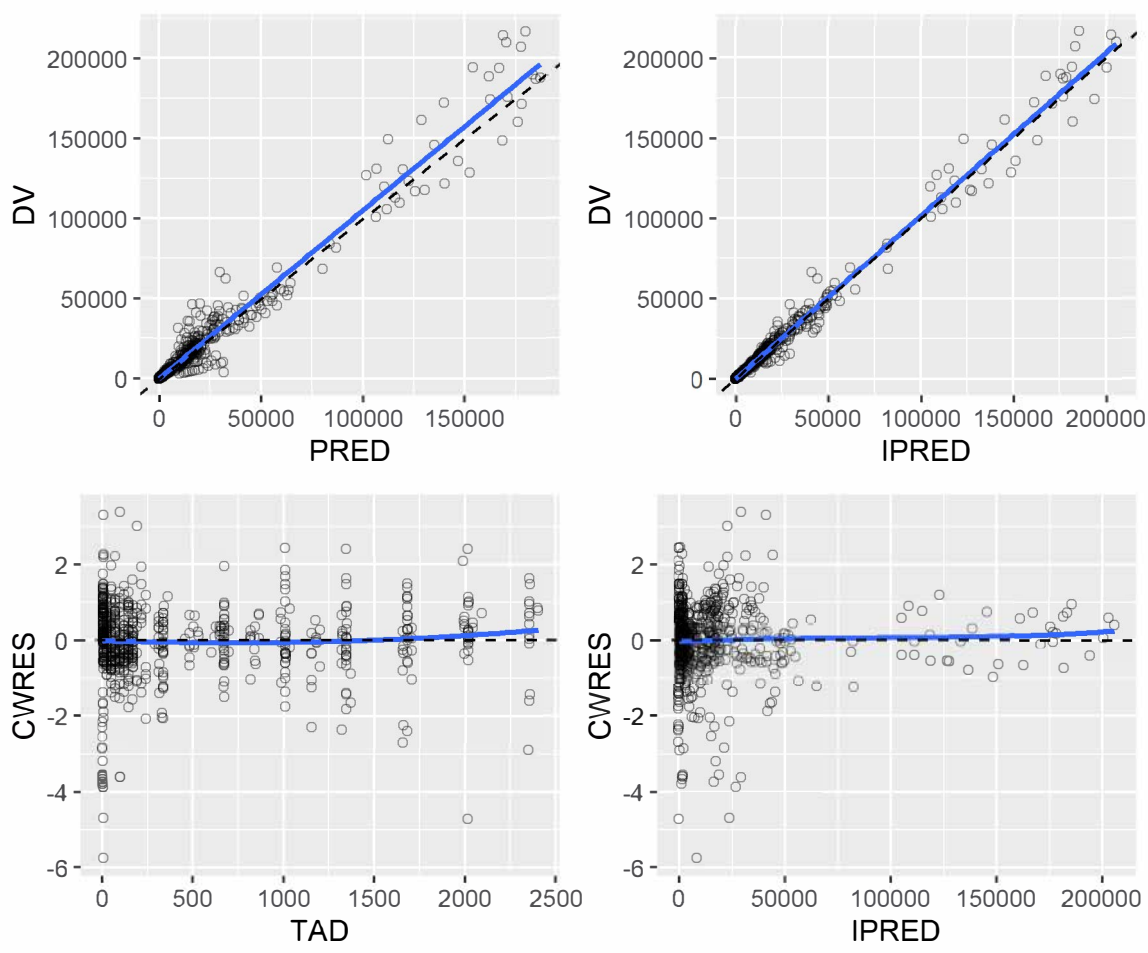

Figure 2 – Goodness of fit plots for the final model
Note: DV – dependent variable; PRED – predicted values; IPRED – individual predicted values; TAD – time after the last dose; CWRES – conditional weighted residuals calculated using the FOCI algorithm.

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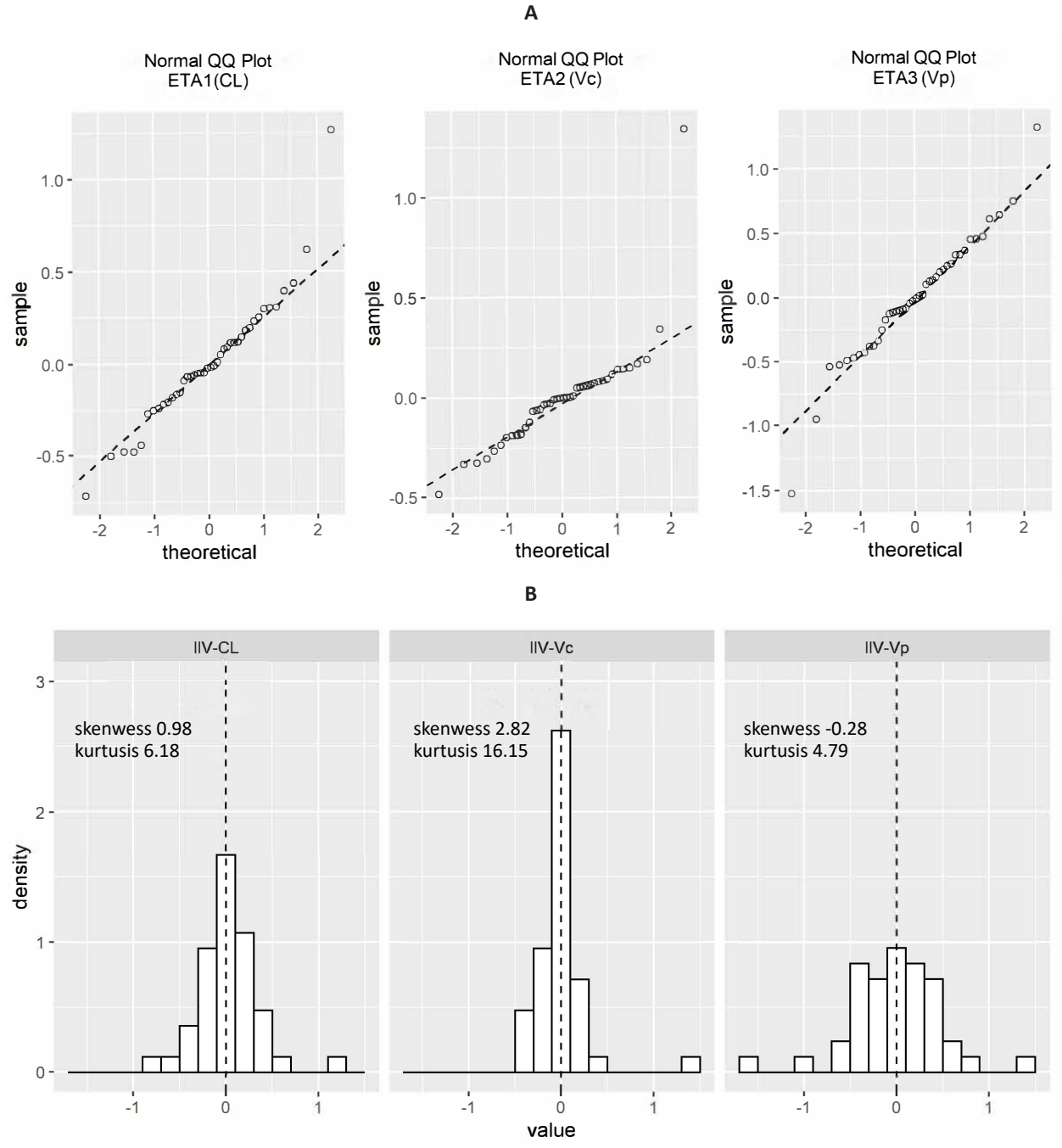

Figure 3 – Assessments of the normality assumption of interindividual variability

Note: ETA = η; IIV – interindividual variability; CL - clearance; Vc – volume of the central chamber; Vp – volume of the peripheral chamber; Normal QQ Plot – quantile-quantile plot for assessing normality of the distribution.

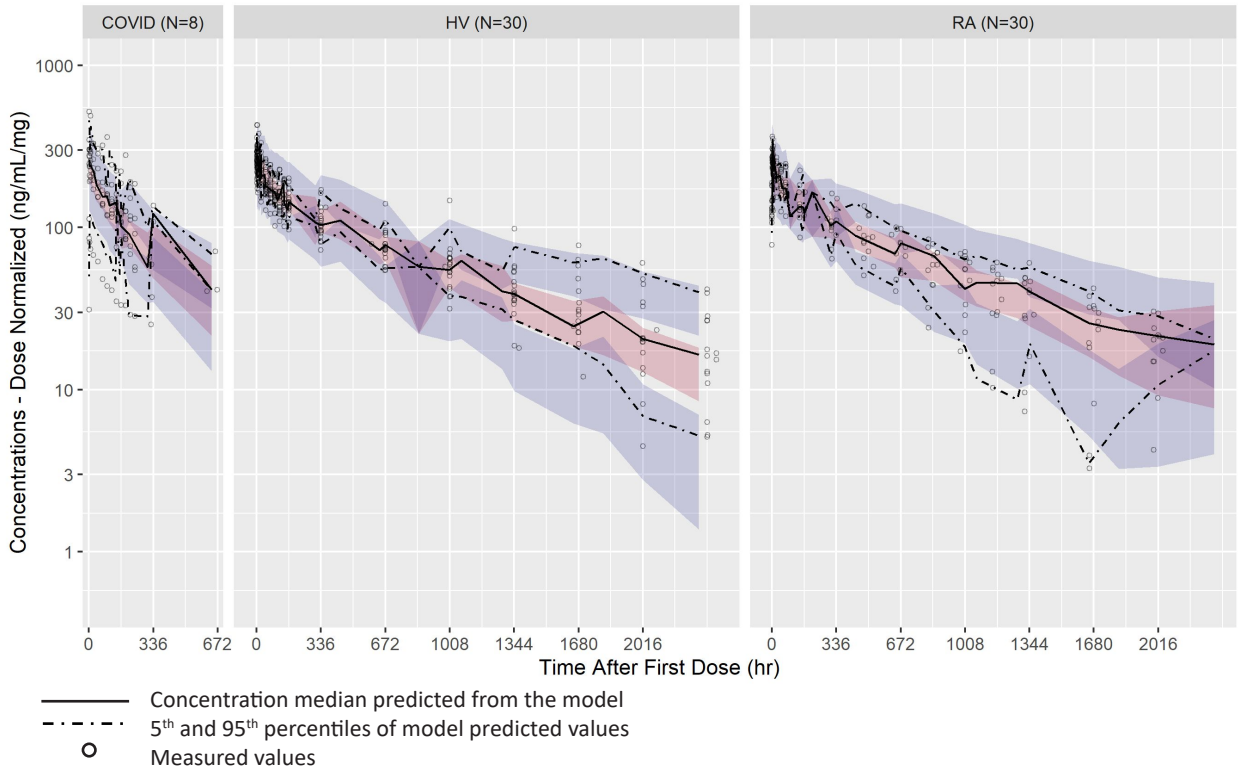

Figure 4 – Graphical representation of observed and predicted pharmacokinetic olokizumab profiles for COVID-19 patients, healthy volunteers, and RA patients

Note: The area marked in pink is the boundaries of the 95% confidence interval for estimating the median; the areas marked in gray are the boundaries of the 95% confidence interval for estimating the 5th and 95th percentiles.

Table 1 – Individual pharmacokinetic olokizumab parameters and mean values

PK parameter	Healthy volunteers [15] 1 mg/kg (76 mg) IV, n = 3[1]	RA patients [16] 1 mg/kg (75 mg) IV, n = 7	COVID-19 patients (RESET study) 128 mg, IV, n=8
C_{max} (µg/ml)			
Mean (±SD)	21.4 (±0.842)	22.28 (±3.9)	40.20 (±18.06)
Geometric mean (CV%)	–	21.98 (17.53)	35.69 (44.93)
T_{max} (h)			
Median	4.00	2.00	6.00
L.Qu., U.Qu.	2.03–4.00	2.0 – 14.0	2,0–18,0
Geometric mean (CV%)	–	4.49 (123.26)	7.44 (159,72)
AUC_{0-t} (h×mcg/ml)			
Mean (±SD)	9 427 (±524)	7 001.58 (±1,259.89)	7 802,19 (±4005,29)
Geometric mean (CV%)	–	6 911.9 (17.99)	6 855.77 (51.34)
$AUC_{0-\infty}$ (h×mcg/ml)			
Mean (±SD)	10 435 (±1,266)	13 979.67 (±3,267.86)	13 117.51 (±9,777.32)
Geometric mean (CV%)	–	13 633.52 (23.38%)	10 600.21 (74.54)
$T_{1/2}$ (days)			
Mean (±SD)	27.9 (±12)	30.66 (±14.2)	13.8 (±10.86)
Geometric mean (CV%)	–	28.13 (46.31)	10.35 (78.65)
CL, l/day			
Mean (±SD)	0.177 (±0.020)	0.145 (±0.03)	0.349 (±0.214)
Geometric mean (CV%)	–	0.143 (20.372)	0.289 (61.275)
Vd, l			
Mean (±SD)	7.08 (±3.04)	6.29 (±2.97)	5.26 (±4.56)
Geometric mean (CV%)	–	5.79 (47.23)	4.33 (86.81)

Notes: SD – standard deviation; CV% – coefficient of variation; L.Qu. – lower quartile (25%); U.Qu. – upper quartile (75%); IV – intravenously; max. – maximum; min. – minimum; n is the number of patients; CL – clearance; Vd – volume of distribution; 1 – the comparison table includes only the data of volunteers administrated with olokizumab at the dose of 1 mg/kg intravenously. A total of 87 volunteers participated in the phase 1 studies, 67 – in the European population (RA0001), 20 – in the Asian (Japanese) population (RA0074).

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Table 2 – Mean pharmacokinetic olokizumab parameters in general population of RA and COVID-19 patients

Parameter		Final model		RSD (%)
		Value	η-shrinkage	
CL (l/day)	θ1	0.154	–	6.8
Vc (l)	θ2	4.1	–	5.6
Q (l/day)	θ3	0.348	–	16.3
Vp (l)	θ4	1.67	–	12.2
Residual error – frequent sampling	θ7	0.167	5.9	–
IIV CL (CV%)	η1	34.2	2.2	–
IIV Vc (CV%)	η2	27.3	2.6	–
IIV Vp (CV%)	η3	56.7	16.0	–
Correlation of random effects				
IIV CL – IIV Vc	$CORR_{1,2}$	0.651	–	–
IIV CL – IIV Vp	$CORR_{1,3}$	0.110	–	–
IIV Vc – IIV Vp	$CORR_{2,3}$	0.512	–	–

Note: RSD – relative standard deviation; CL – total clearance; Vc, Vp – volume of distribution of the central, peripheral, respectively; Q/Vc, Q/Vp – speed constants of exchange between cameras; IIV(CV%) – interindividual variability (coefficient of variation %); θ is a parameter with a fixed value; η is the variability parameter given by a value with a normal distribution; CORR – correlation between random effects.

Table 3 – Effects of individual patients' characteristics

Covariates		Final model	
		Value	RSD (%)
Impact of body weight on CL and Q	θ8	0.654	57.3
Impact of body weight on Vc andVp	θ14	0.498	60.0
Impact of COVID-19 disease on CL	θ16	0.965	23.4

Note: θ – parameter with a fixed value; RSD – relative standard deviation; CL – total clearance; Q – intercompartmental clearance; Vc, Vp – volume of distribution of the central, peripheral, respectively.

Diagnostic plots were used to assess model assumptions and goodness-of-fit; satisfactory η-shrinkage values were obtained, and Visual Predictive Check was performed. The stability of the model, the asymmetry and kurtosis of the η distribution were also evaluated [13, 14].

Population pharmacokinetic olokizumab parameters were evaluated using the First Order Condition Estimation (FOCE) algorithm in NONMEM 7.4 software. The construction of diagnostic plots, the exploratory analysis, and post-processing of the NONMEM output data were performed using R version 3.5.3 software. The analysis was performed in accordance with FDA[6] and EMEA[7] guidelines for population pharmacokinetics.

RESULTS

The mean age of the patients was 56.4 (±10.0) years [45 to 74 years], the majority were males (87.5%), the average body weight of the patients was 87.0 (±15.1) kg, and BMI – 26.8 (±3.4). All patients were Caucasian. In five patients, biosamples were taken at all planned points, in 2 patients the sampling was completed at the point of 366 hours and in 1 – at the point of 240 hours (a withdrawal due to death).

Standard non-compartmental PK parameters from individual studies are presented in Table 1, compared with the results of the previous studies in healthy volunteers and RA patients. After the administration, the drug was distributed fairly fast. In the studied population, C_{max} was reached quite fast and was about 36 μg/ml, the median T_{max} was 6 hours. Further on, the concentration decreased during the entire subsequent observation period. Despite a faster decrease in the concentration compared with the intravenous (IV) olokizumab administration at the dose of 1 mg/kg (mean 75 mg) in RA patients [10], 7 days after the administration, in 7 out of 8 patients, the plasma concentration of olokizumab exceeded 10 mcg/ml; after 14 days, in 5 out of 7 patients, the concentration was above 5 mcg/ml. In this case, the mean $T_{1/2}$ was about 13.8 days, which was significantly lower than when administered intravenously to healthy volunteers (27.9 days) and RA patients (30.66 days).

[6] Guidance for Industry: Population Pharmacokinetics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), February 2022.
[7] EMEA report. Guideline on Reporting the Results of Population Pharmacokinetic Analyses, 2007.

Analysis of individual characteristics influence on olokizumab clearance

A graphical analysis of the goodness-of-fit criteria and a visual assessment of the compliance with the model predictions demonstrated the satisfactory ability of the selected population pharmacokinetic model to describe plasma concentrations of olokizumab (Fig. 2–4).

The average pharmacokinetic olokizumab parameters in the general population of RA and COVID-19 patients, determined on the basis of the developed population pharmacokinetic model, generally corresponded to the previously obtained individual pharmacokinetic parameters in the RA population (clearance 0.153 l/day vs. 0.147 l/day)[8].

The covariates analysis showed that a body weight has the greatest effect on the drug elimination rate (Table 3). After adjusting for albumin and body weight, a COVID-19 disease was found to be an independent significant factor in increasing olokizumab clearance by 96.5% (θ16).

DISCUSSION

The peak intravenous concentration in COVID-19 patients was about 36 μg/mL; it was consistent with the previous data in healthy volunteers and RA patients however, in only two patients T_{max} exceeded 8 hours. Thus, in general, the time to peak concentration was comparable in all studied populations, the observed differences may be associated with differences in the speed and techniques of intravenous infusion of the drug in different studies. Although the rate of elimination and the volume of olokizumab distribution did not significantly differ between healthy volunteers and RA patients, the patients with moderate COVID-19 showed a significantly faster clearance of the drug. The median of $T_{1/2}$ in COVID-19 patients was about 6 days compared to about 30 days in healthy volunteers and RA patients. For a more detailed analysis, a previously developed population pharmacokinetic model based on the results intravenous administration of olokizumab in healthy volunteers and patients with RA program, was adapted to assess the impact of individual patients' characteristics on the drug clearance in COVID-19 patients. It has been shown that a decrease in albumin levels and an increase in body weight are associated with an increase in the rate of olokizumab clearance. Decreased albumin levels are a hallmark of a COVID-19 disease: hypoalbuminemia is observed in 30–50% of hospitalized patients and can serve as an independent predictor of a severe disease and death [23, 24], while average levels of albumin in healthy volunteers and RA patients do not differ. An increased body weight is a risk factor for severe COVID-19, and therefore such patients are more likely to be hospitalized and are disproportionately represented in the study populations. The median body weight of patients in the COVID-19 patient cohort was higher compared to RA patients and healthy volunteers (92, 78 and 76 kg, respectively). Thus, a faster olokizumab clearance in COVID-19 patients may be partly explained by a higher incidence of hypoalbuminemia and the greater body weight of patients. A COVID-19 disease was also independently associated with increased olokizumab clearance, which may be due to the acceleration of protein metabolism in infectious and inflammatory diseases [25], one of the markers of which can serve as a reduced level of albumin. Hypoalbuminemia is a characteristic feature of a COVID-19 disease: it is observed in 30–50% of hospitalized patients and plays an independent predictor of a severe disease and death [17–22], while mean albumin levels do not differ between healthy volunteers and RA patients.

A similar effect, comparable in magnitude, was previously demonstrated for another inhibitor of the IL-6 signaling pathway, tocilizumab, in patients with severe COVID-19 [21]. In the review by Leung E. et al. (2022), 2 routes for the elimination of monoclonal antibodies are described. The first pathway, providing a linear clearance, is associated with proteolytic catabolism of drugs after the administration. The second pathway involves a specific a ligand-receptor (e.g., IL-6 receptor and tocilizumab) binding to both soluble and membrane-bound targets, followed by an internalization and an intracellular degradation. This process provides a non-linear clearance and depends on the relative expression of the target. Therefore, this mechanism may be influenced by patient-specific factors such as the type and severity of the disease. In this case, the linear part of the tocilizumab clearance, apparently, to some extent depends on a body weight.

In the study by Moes D.J.A.R. et al (2021), in patients with severe COVID-19, the clearance (CL) estimate was 0.725 l/day and it was higher than the estimate in adult RA patients (0.2–0.3 l/day), children with systemic juvenile idiopathic arthritis (0.17 l/day), children and adults with a CAR T-induced cytokine release syndrome (0.5 l/day) [26]. Similar trends are shown by the ratio of the olokizumab clearance in patients with moderate

[8] Instructions for drug use Artlegia®. Available from: https://artlegia.com/#close

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COVID-19 (0.349 l/day) and RA patients (0.145 l/day). However, it should be taken into account that the study did not show the feasibility of calculating the dose of tocilizumab based on the body weight of patients, the use of fixed doses is preferable. Given these data, a caution should be exercised when interpreting the study results of this population olokizumab pharmacokinetics. Thus, until further pharmacokinetic data are obtained in COVID-19 patients, a revision of the dosing olokizumab regimen seems unreasonable in this population.

CONCLUSION

After the intravenous administration of olokizumab, during the disease course, in patients with moderate COVID-19, an increase in clearance was demonstrated compared with previously studied populations of healthy volunteers and RA patients. The main contribution to the increased olokizumab clearance is made by the characteristics of the COVID-19 patients population associated with the risk of the severe disease (overweight) and the effect of accelerated protein metabolism due to the severe inflammation, characterized by hypoalbuminemia. At the same time, the contribution of the unidentified factors of the increased clearance associated with a COVID-19 disease, and probably due to the interaction of the mechanism of olokizumab action and COVID-19 pathogenesis, was also observed. However, when administered intravenously at the dose of 128 mg, a therapeutically significant olokizumab level was maintained throughout the acute phase (28 days) of the disease.

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CONFLICT OF INTERESTS

The clinical trial was organized by the sponsor, the JSC “R-Pharm”, the manufacturer and owner of the registration certificate for the drug Artlegia® (olokizumab) dated May 21, 2020. The authors of the article Zinchenko A.V., Dolgorukova A.N., Nikolskaya M.V., Lemak M.S., Filon O.V., Samsonov M.Yu. are employees of the JSC “R-Pharm”. The authors of the article Tavlueva E.V., Zernova E.V., Kutepova M.P., Kostina N.E., Lesina V.S. are physicians-researchers of the scientific centers of Voronezh Regional Clinical Hospital No. 1 (Center No. 03) and Inozemtsev City Clinical Hospital, Department of Health of the City of Moscow (Center No. 04) according to the protocol “Multicenter open randomized study of efficacy and safety of a new regimen for the use of the drug Artlegia® (INN: olokizumab) in patients with a coronavirus infection (COVID-19) with signs of hyperinflammation, sponsored by the JSC “R-Pharm”.

AUTHORS’ CONTRIBUTION

Tavlueva E.V., Zernova E.V., Kutepova M.P., Kostina N.E., Lesina V.S. – implementation of the experimental part of the study; Mould D.R., Ito K. – development of population pharmacokinetic model; Zinchenko A.V. – analytical processing of the obtained results; Dolgorukova A.N. – statistical processing of the study results; Nikolskaya M.V. – text writing and editing; Lemak M.C. – planning and description of the pharmacokinetic model; Filon O.V. – development of research design, text writing and editing; Samsonov M.Yu. – aim setting, research design development.

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