# EXPERIENCE OF TOCILIZUMAB IN HOSPITAL PATIENTS WITH MODERATE COVID-19

Burgasova OA[1,2] ✉, Dolinniy SV[3], Tetova VB[1], Ogarkova DA[2], Odnoralov MA[1], Bacalin VV[1], Smetanina SV[3], Antipyat NA[3], Taranova MV[4]

[1] Peoples Friendship University of Russia, Moscow, Russia

[2] Gamaleya National Research Center for Epidemiology and Microbiology, Moscow, Russia

[3] Clinical Hospital for Infectious Diseases №1, Moscow, Russia

[4] Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Severe form of COVID 19 has been linked to the phenomenon of dysregulated inflammation with excessive cytokine release and elevated interleukin 6 (IL6) levels. Suppressive agents enabling specific inhibition of cytokines, notably monoclonal antibodies to IL6 and its receptors, have been applied as a rescue therapy in COVID 19 despite the underexplored clinical scope for these biologic medications. This study aimed to evaluate the clinical utility of IL6 receptor antagonist tocilizumab in moderate symptomatic COVID 19 prone to aggravation. The retrospective cohort study enrolled two groups of hospitalized patients (a total of *n* = 72) diagnosed with moderate COVID-19. The main group received a single 400 mg dose of tocilizumab (TCZ) on top of standard therapy. The comparative analysis included statistical evaluation for a number of clinical and laboratory parameters at reference time points and disease outcomes with regard to treatment strategy. Overall, TCZ administration provided no advantages in terms of oxygen supplementation status, disease progression, or survival. Lethal cases constituted 19.2% (10 pts) and 5% (1 pt) in TCZ and comparison groups, respectively. The results indicate that administration of monoclonal antibody drugs in hospital patients with COVID-19 must follow differential schemes with regard to the disease severity and comorbidities, as well as proper commencement schedules.

**Keywords:** COVID-19, SARS-CoV-2, acute respiratory distress syndrome (ARDS), interleukin 6 (IL6) inhibitors, tocilizumab, dexamethasone

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**Compliance with ethical standards:** the study was approved by the ethics committee at the Clinical Hospital for Infectious Diseases №1 (Protocol 1 of January 11, 2021); all participants provided informed consent for the study.

✉ **Correspondence should be addressed:** Olga A. Burgasova
Volokolamskoe sh., 47, str. 8, korp. 5, Moscow, 125310, Russia; olgaburgasova@mail.ru

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# ОПЫТ ПРИМЕНЕНИЯ ТОЦИЛИЗУМАБА У СТАЦИОНАРНЫХ ПАЦИЕНТОВ СО СРЕДНЕТЯЖЕЛЫМ ТЕЧЕНИЕМ COVID-19

О. А. Бургасова[1,2] ✉, С. В. Долинный[3], В. Б. Тетова[1], Д. А. Огаркова[2], М. А. Одноралов[1], В. В. Бакалин[1], С. В. Сметанина[3], Н. А. Антипят[3], М. В. Таранова[4]

[1] Российский университет дружбы народов, Москва, Россия

[2] Национальный исследовательский центр эпидемиологии и микробиологии имени Н. Ф. Гамалеи, Москва, Россия

[3] Инфекционная клиническая больница № 1, Москва, Россия

[4] Первый Московский государственный медицинский университет имени И. М. Сеченова (Сеченовский университет), Москва, Россия

Осложненное течение COVID-19 ассоциировано с феноменом нерегулируемого воспаления, синдромом избыточного выброса цитокинов, в том числе повышением уровня интерлейкина-6 (IL6). Для лечения пациентов с COVID-19 стали активно применять супрессивные средства с векторным блокированием цитокинов — моноклональные антитела к IL6 и его рецепторам. Терапевтическая эффективность различных биологических средств при COVID-19 пока недостаточно изучена. Целью исследования было оценить влияние антагониста рецептора IL6 тоцилизумаба на клиническое течение COVID-19 в сравнении с поддерживающей кортикостероидной терапией. В ретроспективном когортном исследовании наблюдали две группы пациентов (*n* = 72) со среднетяжелым течением COVID-19 и риском прогрессирования заболевания. Пациентам основной группы к стандартной терапии однократно вводили тоцилизумаб в дозе 400 мг. Проведен сравнительный анализ основных параметров клинико-лабораторного профиля и исходов заболевания в контрольных временных точках при использовании различных лечебных стратегий. Результаты применения тоцилизумаба у пациентов со среднетяжелым течением COVID-19 не продемонстрировали преимуществ его использования для снижения потребности в дополнительной кислородной поддержке и риска прогрессирования заболевания до тяжелой формы, а также числа летальных исходов по сравнению с поддерживающей терапией. Число летальных случаев составило 10 (19,2%) и 1 (5%) в группах с применением тоцилизумаба и поддерживающей терапии соответственно. Использование препаратов моноклональных антител у пациентов с COVID-19, возможно, требует избирательного подхода с учетом не только степени тяжести заболевания, коморбидности, но и сроков начала введения биологических супрессивных средств.

**Ключевые слова:** COVID-19, SARS-CoV-2, острый респираторный дистресс-синдром (ОРДС), ингибитор IL6, тоцилизумаб, дексаметазон

**Вклад авторов:** О. А. Бургасова — инициатор исследования, дизайн, руководство клинической частью, подготовка рукописи; С. В. Долинный — анализ литературных источников, клинические наблюдения, обработка результатов; В. Б. Тетова — анализ литературных источников, редактирование статьи; Д. А. Огаркова — статистический анализ; М. А. Одноралов, В. В. Бакалин — клинические наблюдения, обработка клинических и лабораторных данных; С. В. Сметанина — концепция исследования; Н. А. Антипят — руководство клинической частью исследования; М. В. Таранова — анализ литературных источников, обработка результатов.

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✉ **Для корреспонденции:** Ольга Александровна Бургасова
ул. Волоколамское шоссе, д. 47, стр. 8, корп. 5, г. Москва, 125310, Россия; olgaburgasova@mail.ru

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The coronavirus pandemic remains a major challenge to global healthcare, responsible for over 4 million deaths as of October 2021 [1]. Despite the enormous vaccination efforts, the problem will persist due to the high mutation capacity of the SARS-CoV-2 virus.

Immune response plays a pivotal role in individual susceptibility to infectious diseases. Dysfunctional immune reactions are responsible for severe respiratory distress syndrome in viral pathologies, including the acute viral respiratory infections. The excessive release of pro-inflammatory cytokines, termed "cytokine storm", is the critical immunological event leading to severe clinical syndrome, a grave complication of infectious and inflammatory diseases. The cytokine storm and acute respiratory distress syndrome (ARDS) are directly related to adverse prognosis in COVID-19 [2–10].

The availability of safe and effective therapeutics for the treatment of hospitalized patients with COVID-19 remains a major clinical issue, which is far from being solved decidedly. The progress will depend on clinical trials for antiviral and anti-inflammatory drugs including monoclonal antibodies.

As demonstrated in a number of cohort and clinical studies, properly scheduled administration of immunomodulatory agents to patients with COVID-19 can substantively improve the clinical status, reduce the hospital stay, and ultimately alleviate the risk of lethal outcome [11]. Several studies on the therapeutic efficacy of neutralizing monoclonal antibodies in patients with COVID-19 have shown significant reduction of SARS-CoV-2 viral loads and prevention of the disease progression [12–15]. One of such molecules, tocilizumab (TCZ), specifically targets the receptor of interleukin 6 (IL6). Systematic reviews suggest that rational use of TCZ may prevent the irreversible lung damage in severely and critically ill patients with COVID-19 [16].

Meta-analysis of available evidence on the efficacy of TCZ in hospitalized patients with COVID-19, encompassing eight randomized clinical studies ($n$ = 5,340) and 28 observational cohort studies ($n$ = 15,484), revealed a negative association between TCZ therapy and the demand for mechanical ventilation at a high level of significance. In addition, TCZ therapy has been associated with reduced probability of adverse outcome and reduced risks of secondary infections in patients with COVID-19, albeit at a medium level of significance [17]. On the other hand, a systematic review on the use of TCZ for the treatment of COVID-19, based on the results of three indirect preclinical studies and 28 clinical studies enrolling 5,776 patients with COVID-19 and viral pneumonia/sepsis treated with TCZ before June 20, 2020, failed to confirm the rationale due to the scarcity and controversy of the clinical evidence [18]. Yet another three clinical studies on IL6 antagonists, RCT-TCZ-COVID, CORIMUNO, and STOP-COVID, unanimously conclude that the most promising member of this pharmacological group, TCZ, has negligible efficacy in mild or moderate COVID-19 [19–21]. The benefits of TCZ in severe COVID-19 are conditional, and their dedicated scrutiny will require extra randomized trials enrolling large clinical samples at different stages of pathogenesis.

This study aimed to evaluate the therapeutic efficacy of TCZ as a part of combination therapy in hospitalized patients with moderate COVID-19.

## METHODS

This retrospective cohort study was carried out in a city clinical hospital for infectious diseases between January 11, 2021 and December 31, 2021. The initial demographic, clinical, and epidemiological data were retrieved from printed and electronic medical records. The diagnosis of COVID-19 was conclusively confirmed by positive results of real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in nasopharyngeal swabs.

The observations encompassed 72 inpatients diagnosed with moderate symptomatic COVID-19 in accordance with the 2021 WHO guidelines. The patients presented with certain risk factors for aggravation of the disease and were hospitalized on day 8 ± 3.5 since the initial symptoms. The patients were assigned into two groups: the main group ($n$ = 52) received tocilizumab (TCZ) on top of standard therapy and the comparison group ($n$ = 20) received standard therapy with dexamethasone (DMX).

The inclusion criteria were as follows: moderate symptomatic COVID-19 with developed pneumonia and various comorbidities, risk factors for disease aggravation (age ≥ 60, diabetes, chronic respiratory and/or cardiovascular conditions, arterial hypertension, and/or presentation with X-ray signs of pneumonia). The exclusion criteria were the absence of characteristic symptoms of COVID-19, the absence of pneumonia, and the use of alternative biologic medications.

The clinical status was assessed on the following basis: clinical blood tests including leukocyte differential and erythrocyte sedimentation rate; biochemical blood tests including C-reactive protein (CRP) levels; chest X-ray scan for the signs of pneumonia; and pulse oximeter readings ($SpO_2$). Importantly, the positive RT-PCR test for SARS-CoV-2 in a nasopharyngeal swab collected at admission was a prerequisite for the final diagnosis of COVID-19. The data analysis involved between-the-group comparisons of survival rates, as well as clinical and laboratory profiling before (baseline data) and after the treatment (clinical and laboratory indicators collected at reference time points after the medications had been administered).

Patients of the main group (TCZ group, $n$ = 52) were admitted to inpatient care units at different time points with regard to initial symptoms: 9 pts (17.3%) were hospitalized on day 1–5, the majority (32 pts, 61.5%) on day 6–10, 8 pts (15.4%) on day 11–15, and 3 pts (5.8%) on > 15 day of the illness. Age of patients in the main group constituted 30–50 years (7 pts, 13.5%), 51–70 years (24 pts, 46.2%), and > 71 years (21 pt, 40.3%). The main group included 19 (36.5%) men and 33 (63.5%) women.

Patients of the main group received TCZ at a single 400 mg dose administered by intravenous drip on day 10 ± 3.7 of the illness on top of standard scheme in compliance with the current regulatory guidelines. The dynamic observation encompassed clinical and laboratory-instrumental indicators.

Patients of the comparison group ($n$ = 20), who received the standard scheme with DMX, were also admitted at different time points with regard to the disease onset: 4 pts (20%) were hospitalized on day 1–5, the majority (13 pts, 65%) on day 6–10, 2 pts (10%) on day 11–15, and 1 pt was hospitalized on > 15 day of the illness. Age of patients in the comparison group constituted 51–70 years (9 pts, 45%) and > 71 years (11 pts, 55%). The comparison group included 10 (50%) men and 10 (50%) women. According to the guidelines of the Ministry of Health of the Russian Federation, all patients of the comparison group received DMX infusions on day 8 ± 3.7, 4 mg 2 times a day. Structure of clinical symptoms for the two groups is given in Table 1; baseline data, dynamics of clinical and laboratory parameters, and outcomes are given in Table 2. The groups were similar in age structure (68 [59–80.5] vs. 72.5 [64.5–82] years; $p$ = 0.308), hospitalization time point (day 8 [6–10] vs. 8 [6.5–8.5] of the illness; $p$ = 0.505), and initial laboratory parameters.

**Table 1.** Structure of clinical symptoms in patients receiving tocilizumab vs. standard therapy (+dexamethasone)

| Symptoms | Tocilizumab | | Maintenance therapy/dexamethasone | |
|---|---|---|---|---|
| | (*n* = 52) | | (*n* = 20) | |
| Fatigue | *n* = 52 | 100% | *n* = 20 | 100% |
| Headache | *n* = 3 | 5.8% | *n* = 0 | 0% |
| Myalgia | *n* = 2 | 3.8% | *n* = 3 | 15% |
| Chills | *n* = 46 | 88.5% | *n* = 14 | 70% |
| Rash | *n* = 2 | 3.8% | *n* = 1 | 5% |
| Oropharyngeal hyperemia | *n* = 3 | 5.8% | *n* = 1 | 5% |
| Sore throat | *n* = 5 | 9.6% | *n* = 1 | 5% |
| Nasal congestion | *n* = 0 | 0% | *n* = 0 | 0% |
| Dry cough | *n* = 33 | 63.5% | *n* = 12 | 60% |
| Wet cough | *n* = 4 | 7.7% | *n* = 0 | 0% |
| Abdominal pain | *n* = 3 | 5.8% | *n* = 1 | 5% |
| Nausea/vomiting | *n* = 9 | 17.3% | *n* = 0 | 0% |
| Diarrhea | *n* = 11 | 21.2% | *n* = 2 | 10% |
| Fainting | *n* = 1 | 1.9% | *n* = 2 | 10% |
| Vertigo | *n* = 7 | 13. 5% | *n* = 1 | 5% |
| Meningeal signs | *n* = 0 | 0% | *n* = 0 | 0% |
| Dysosmia | *n* = 4 | 7.7% | *n* = 1 | 5% |
| Dysgeusia | *n* = 1 | 1.9% | *n* = 0 | 0% |

The main group received the biologic medication on day 10 [8–12] of the illness, whereas the comparison group received standard therapy plus DMX starting from day 8 [5.5–10] of the illness. Equivalent proportions of patients in both groups received steroids (100%). None of the patients in both groups received other immunosuppressive drugs (e.g. levilimab, baricitinib).

Statistical analysis of the data was carried out using IBM SPSS Statistics 26 (IBM; USA). Distributions of most quantitative variables differed from normal ($p > 0.05$; Shapiro–Wilk test); these were described nonparametrically as median [interquartile range]. The comparisons were carried out using Mann–Whitney test for independent samples (groups), Wilcoxon rank test for dependent samples, and Pearson's $\chi^2$ test or Fisher's exact test for categorical data.

## RESULTS

The analysis of clinical and laboratory parameters revealed significant 10-fold decrease in serum CRP to 7 mg/L (3.5–41.5 mg/L) at 24 h after TCZ infusion ($p < 0.001$). In addition, the use of TCZ was associated with significant increase in platelet counts at 24 h after the infusion ($p < 0.001$). At the same time, the main group showed adverse dynamics for LDH, progressively increased to 341 U/L (280–522 U/L, $p < 0.05$), and no dynamics for oxygen saturation levels. Dynamics of clinical and laboratory parameters for the main group are given in Table 3.

The comparison group, treated with DMX only, showed identical positive dynamics for CRP (11-fold reduction compared with baseline measurements, $p = 0.001$) and platelet counts (to 274.5, 222–357, $p = 0.002$) during the same reference period, and no dynamics for oxygen saturation. Dynamics of clinical and laboratory parameters for the comparison group are given in Table 4.

The lethality constituted 19.2% for the main group (10 pts died in the inpatient care unit, including 1 pt (1.9%) aged < 60 years and 9 pts (17.3%) aged > 60 years), and 5% for the comparison group (1 pt aged > 60 years).

## DISCUSSION

Therapeutic use of monoclonal antibody drugs in patients with COVID-19 has multiple shortcomings including the understudied safety profiles, high costs, and unproved efficacy. According to WHO recommendations, the use of TCZ is only justified in critically ill patients with COVID-19. By contrast, clinical guidelines adopted in Russia suggest using this medication for a broader clinical spectrum including moderate COVID-19 in hospitalized patients with risk burden [22]. To date, many specialized inpatient care units practise the use of TCZ as first line treatment for COVID-19 despite the in many ways unconvincing results of clinical trials and rather controversial clinical experience.

In this study on clinical efficacy of TCZ, encompassing individuals with moderate COVID-19 and risks for aggravation, we monitored known indicators of disease progression, including of CRP and SpO2 levels. Positive dynamics of certain clinically validated parameters (CRP, platelets) after TCZ administration should be noted.

However, we observed no significant reduction in the rate of disease progression to severe form in response to TCZ. In particular, respiratory support was required in 71.2% (37 pts) of the main group and 45% (9 pts) of the comparison group. Aggravation of the respiratory failure syndrome was encountered in 9.6% (5 pts) of the main group and 5% (1 pt) of the comparison group. The lethality constituted 19.2% (10 pts) in the main group and 5% (1 pt) in the comparison group.

The increase in IL6 levels and sharp decrease in CRP levels observed in TCZ-treated patients of our cohort

**Table 2.** Baseline data, dynamics of clinical and laboratory parameters, and clinical outcomes in patients receiving tocilizumab vs. standard therapy (+dexamethasone)

| Parameter | Tocilizumab ($n$ = 52) | Maintenance therapy/ dexamethasone ($n$ = 20) | $p$ |
|---|---|---|---|
| Demographic data | | | |
| Age | 68 [59–80.5] | 72.5 [64.5–82] | 0.308 (Mann–Whitney test) |
| Sex | M: 19 (36.5%) | M: 10 (50%) | |
| | F: 33 (63.5%) | F: 10 (50%) | |
| Hospitalized, day of illness | 8 [6–10] | 8 [6.5–8.5] | 0.505 (Mann–Whitney test) |
| Medication administered, day of illness | 10 [8–12] | 8 [5.5–10] | 0.022* (Mann–Whitney test) |
| Comorbidities | | | |
| Arterial hypertension | 39 75% | 16 80% | 0.764 (Pearson's $\chi^2$ test) |
| Cardiovascular disorders | 25 48% | 14 70% | 0.118 (Pearson's $\chi^2$ test) |
| Diabetes mellitus | 12 23% | 6 30% | 0.762 (Pearson's $\chi^2$ test) |
| Chronic respiratory disorders | 11 21% | 3 15% | 0.744 (Fisher's exact test) |
| Obesity | (known for 46) | (known for 16) | 0.020* (Pearson's $\chi^2$ test) |
| | 28 61% | 4 | |
| | | 25% | |
| Clinical indicators | | | |
| Temperature, initially | 36.8 [36.6–37.4] | 36.8 [36.6–37.35] | 0.845 (Mann–Whitney test) |
| Temperature, 4 days after treatment | 36.6 [36.45–36.8] | 36.65 [36.5–36.8] | 0.978 (Mann–Whitney test) |
| Saturation, initially | 95.5 [93–96.5] | 95.5 [94.5–97] | 0.318 (Mann–Whitney test) |
| Saturation, 4 days after treatment | 96 [94–97] | 96 [95–98] | 0.247 (Mann–Whitney test) |
| Laboratory test results | | | |
| Leukocytes, total, initially | 7 [5.2–9] | 7.05 [6.20–10.05] | 0.427 (Mann–Whitney test) |
| Leukocytes, total, 4 days after treatment | 5.7 [4.2–11] | 8.35 [5.8–10.5] | 0.075 (Mann–Whitney test) |
| Lymphocytes, total, initially | 1.23 [0.84–1.57] | 1.24 [0.85–1.64] | 0.832 (Mann–Whitney test) |
| Lymphocytes, total, 4 days after treatment | 1.09 [0.70–1.75] | 1.62 [1.14–1.84] | 0.107 (Mann–Whitney test) |
| CRP, initially | 72 [28.5–130.5] | 74 [39.5–105.5] | 0.977 (Mann–Whitney test) |
| CRP, 24 h after treatment | 7 [3.5–41.5] | 6 [5–12.5] | 0.945 (Mann–Whitney test) |
| Ferritin, initially | 499.5 [251–1033] | 319 [295–399] | 0.872 (Mann–Whitney test) |
| Ferritin, 24 h after treatment | 708 [375–904] | 1252 [783–1500] | 0.127 (Mann–Whitney test) |
| Interleukin, initially | 37 [19–182] | 12 [7–439] | 0.479 (Mann–Whitney test) |
| Interleukin, 24 h after treatment | 319 [167–807.5] | 16 [8–37] | 0.017* (Mann–Whitney test) |
| Procalcitonin, initially | 0.14 [0.08–0.22] | 0.23 [0.10–6.10] | 0.497 (Mann–Whitney test) |
| Procalcitonin, 24 h after treatment | 0.145 [0.06–0.16] | 0.14 [0.08–0.18] | 0.859 (Mann–Whitney test) |
| D-dimer, initially | 359 [189–937] | 391.5 [163–1193] | 0.903 (Mann–Whitney test) |
| D-dimer, 24 h after treatment | 385 [297–1130] | 332 [ 252–1009] | 0.618 (Mann–Whitney test) |
| LDH, initially | 312 [ 275–422] | 385 [265–443] | 0.737 (Mann–Whitney test) |
| LDH, 24 h after treatment | 341 [280–522] | 245 [197–324] | 0.005* (Mann–Whitney test) |
| Platelets, initially | 156 [135.5–193.5] | 172 [143–185] | 0.499 (Mann–Whitney test) |
| Platelets, 24 h after treatment | 231 [175–300] | 274.5 [222–357] | 0.099 (Mann–Whitney test) |
| Lethality | 10 (19.2%) | 1 (5%) | 0.275 (Fisher's exact test) |

indicates an improvement in hyperinflammatory status, consistently with a systematic review on clinical utility of this biologic medication in COVID-19 at the level of individual patient data including baseline records, laboratory tests, and outcomes [23].

In this study, we had no means to identify the entire complex of causal factors that determined the course of the disease for each patient individually. Apparently, one of the key adverse factors was delayed hospitalization, when the time had already been lost and the aggravation was inevitable. This point is consistent with the reported association between higher demand for oxygen support and delayed commencement of TCZ therapy. It can be speculated that earlier administration of TCZ may effectively prevent or alleviate the generalized inflammation syndrome [21, 23]. The low anti-covid efficacy of TCZ in certain settings may also involve miscellaneous understudied factors. For example, in this study we disregarded the possible impacts of viral

**Table 3.** Dynamics of clinical and laboratory parameters in patients treated with tocilizumab

| Parameter | Initially | After treatment | *p* |
|---|---|---|---|
| Body temperature | 36.8 [36.6–37.4] | 36.6 [36.45–36.8] | < 0.001* (Wilcoxon test for dependent samples) |
| Oxygen saturation | 95.5 [93–96.5] | 96 [94–97] | 0.161 (Wilcoxon test for dependent samples) |
| Leukocytes | 7 [5.2–9] | 5.7 [4.2–11] | 0.945 (Wilcoxon test for dependent samples) |
| Lymphocytes | 1.23 [0.84–1.57] | 1.09 [0.70–1.75] | 0.637 (Wilcoxon test for dependent samples) |
| CRP | 72 [28.5–130.5] | 7 [3.5–41.5] | < 0.001* (Wilcoxon test for dependent samples) |
| Ferritin | 499.5 [251–1033] | 708 [375–904] | 0.859 (Wilcoxon test for dependent samples) |
| Interleukin | 37 [19–182] | 319 [167–807.5] | 0.144 (Wilcoxon test for dependent samples) |
| Procalcitonin | 0.14 [0.08–0.22] | 0.145 [0.06–0.16] | 0.498 (Wilcoxon test for dependent samples) |
| D-dimer | 359 [189–937] | 385 [297–1130] | 0.878 (Wilcoxon test for dependent samples) |
| LDH | 312 [275–422] | 341 [280–522] | 0.020* (Wilcoxon test for dependent samples) |
| Platelets | 156 [135.5–193.5] | 231 [175–300] | < 0.001* (Wilcoxon test for dependent samples) |

**Table 4.** Dynamics of clinical and laboratory parameters in patients treated with standard therapy (+dexamethasone)

| Parameter | Initially | After treatment | *p* |
|---|---|---|---|
| Body temperature | 36.8 [36.6–37.35] | 36.65 [36.5–36.8] | 0.005 (Wilcoxon test for dependent samples) |
| Oxygen saturation | 95.5 [94.5–97] | 96 [95–98] | 0.810 (Wilcoxon test for dependent samples) |
| Leukocytes | 7.05 [6.20–10.05] | 8.35 [5.8–10.5] | 0.140 (Wilcoxon test for dependent samples) |
| Lymphocytes | 1.24 [0.85–1.64] | 1.62 [1.14–1.84] | 0.121 (Wilcoxon test for dependent samples) |
| CRP | 74 [39.5–105.5] | 6 [5–12.5] | 0.001* (Wilcoxon test for dependent samples) |
| Ferritin | 319 [295–399] | 1252 [783–1500] | 1.000 (Wilcoxon test for dependent samples) |
| Interleukin | 12 [7–439] | 16 [8–37] | paired values available for one patient only |
| Procalcitonin | 0.23 [0.10–6.10] | 0.14 [0.08–0.18] | paired values available for one patient only |
| D-dimer | 391.5 [163–1193] | 332 [ 252–1009] | 0.500 (Wilcoxon test for dependent samples) |
| LDH | 385 [265–443] | 245 [197–324] | 0.893 (Wilcoxon test for dependent samples) |
| Platelets | 172 [143–185] | 274.5 [222–357] | 0.002* (Wilcoxon test for dependent samples) |

mutagenesis and viral loads due to technical limitations and small size of the cohort. Identification of other factors interfering with TCZ therapy should rely on larger trials that account for viral mutations.

The analysis accounted for key baseline factors including age, sex, and comorbidities. During the observation period, the protocols for management of moderate COVID-19 underwent no significant alterations; however, there was a spread of new SARS-CoV-2 variants in many countries including Russia. A number of limitations of our study include, first of all, smaller size of the comparison group compared with the main group. Secondly, the research was confined to a single hospital and the long-term results after redirection to outpatient facilities were disregarded. In addition, despite the mandatory confirmation of the diagnosis by RT-PCR test, the analysis disregarded SARS-CoV-2 mutations and viral loads.

## CONCLUSIONS

This retrospective cohort study demonstrated negligible advantages of tocilizumab in hospitalized patients with moderate symptomatic COVID-19 with regard to disease aggravation risks and lethality. The lack of efficacy may reflect the delayed commencement of the therapy. The data contributes to the cumulative clinical evidence on the use of monoclonal antibody drugs as the basis for clinical guidelines. Advanced specification of antiviral strategies (biologic, generic, etc.) in various groups of patients with COVID-19 will require further efforts.

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