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Sarilumab is not Inferior to Tocilizumab in the Treatment of Cytokine Release Syndrome in COVID-19

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Aim: Cytokine release syndrome (CRS) is a dangerous complication of the new coronavirus infection (COVID-19). The study aimed to compare sarilumab (SAR group) with tocilizumab (TOC group) and patients without anticytokine treatment (CON group) in treatment of CRS in COVID-19.
Materials and methods. The retrospective real-life study included COVID-19 patients with C-reactive protein (CRP) level > 60 mg/L.
Results. We enrolled 24 patients in SAR group, 27 patients in TOC group and 47 patients in CON group. Mortality was lower in SAR and TOC groups than in CON group (12.5 and 14.8 % vs. 31.9 %; $p = 0.021$ and $p = 0.031$) with no difference between SAR and TOC groups (p = 0.389). SAR patients unlike TOC patients required intensive care unit admission less frequently than CON patients (16.7 and 25.9 % vs. 46.3 %; $p = 0.013$ and $p = 0.077$). An increase in oxygen saturation was observed in SAR and TOC groups ($p = 0.001$ and $p = 0.004$; greater in SAR group, $p = 0.022$), but not in CON group ($p = 0.764$) in 7–10 days after administration of these drugs. The decrease in CRP level was greater in SAR and TOC groups than in CON group ($p = 0.016$ and $p < 0.011$), with no difference between SAR and TOC groups ($p = 0.236$).
Conclusion. Sarilumab is not inferior to tocilizumab in COVID-19.
Keywords: coronavirus, cytokine release syndrome, interleukin-6, tocilizumab, sarilumab
Conflict of interest: the authors declare that there is no conflict of interest.

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Сарилумаб не уступает тоцилизумабу в лечении синдрома выброса цитокинов, вызванного COVID-19

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Цель исследования. Синдром выброса цитокинов (СВЦ) является опасным осложнением новой коронавирусной инфекции (COVID-19). Целью исследования было сравнить эффективность сарилумаба (группа «SAR») и тоцилизумаба (группа «TOC») в лечении этого осложнении COVID-19.
Материалы и методы. В ретроспективное исследование были включены пациенты с COVID-19, имевшие содержание С-реактивного белка (СРБ) в крови > 60 мг/л.
Результаты. В группу «SAR» были включены 24 пациента, в группу «TOC» — 27 пациентов. Кроме того, 47 пациентов с СВЦ не получали антицитокиновой терапии (группа «CON»). Смертность в группах «SAR» и «TOC» была ниже, чем в группе «CON» (12,5 и 14,8 % vs. 31,9 %; $p = 0,021$ и $p = 0,031$), без значимых различий между группами «SAR» и «TOC» ($p = 0,389$). Пациенты группы «SAR», в отличие от пациентов группы «TOC», реже нуждались в госпитализации в отделение реанимации, чем пациенты группы «CON» (16,7 и 25,9 % vs. 46,3 %; $p = 0,013$ и $p = 0,077$). Через 7–10 дней после введения тоцилизумаба/сарилумаба значимое увеличение насыщения артериальной крови кислородом наблюдалось у пациентов в группах «SAR» и «TOC» ($p = 0,001$ и $p = 0,004$; больше в группе «SAR», $p = 0,022$), но не за тот же период в группе «CON» ($p = 0,764$). Снижение уровня СРБ через 7–10 дней после введения препарата было больше в группах «SAR» и «TOC», чем в группе «CON» ($p = 0,016$ и $p < 0,011$), без значимых различий между группами «SAR» и «TOC» ($p = 0,236$).

Вывод. Сарилумаб не уступает тоцилизумабу в лечении СВЦ при COVID-19.
Ключевые слова: коронавирус, синдром выброса цитокинов, интерлейкин-6, тоцилизумаб, сарилумаб, цитокиновый шторм
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Introduction

The new coronavirus infection (COVID-19) has become a new challenge for medicine. It can have some severe complications, among which the cytokine release syndrome is one of the most dangerous [1–3]. The main role in its development has interleukin-6 (IL-6) [2, 3]. Several studies of low quality have shown effectiveness of IL-6 antagonist tocilizumab in its treatment [4–6]. This was the basis for a series of randomized controlled trials (RCT), meta-analyzes of which confirmed that tocilizumab is effective in COVID-19 [7–11].

Sarilumab is another monoclonal antibody against IL-6 receptors [12] whose effectiveness in COVID-19 has been much less studied. The potential effect of this drug on COVID-19 has been described in some uncontrolled studies [13–15]. A large RCT showed that sarilumab had no significant effect on the prognosis of patients with COVID-19 pneumonia who required oxygen supplementation or mechanical ventilation [16]. However, the main target of this drug is not pneumonia or respiratory failure, but the cytokine release syndrome. This may explain the negative result of this study. Several other RCTs investigating the effect of sarilumab on COVID-19 have been claimed, but none of these data compare sarilumab with tocilizumab [17].

Thus, the efficacy of sarilumab in the treatment of COVID-19 remains poorly understood, and there are no studies comparing its efficacy and safety with tocilizumab, which became the aim of our work.

Materials and methods

This was a retrospective real-life open off-label study. All patients signed an informed consent for the use of off-label drugs. The study was approved by the local ethical committee of Sechenov University.

The study included patients admitted to the Clinic of internal diseases, gastroenterology and hepatology with suspected COVID-19 in accordance with the recommendations of the World health organization [18] from April to July 2020 and had cytokine release syndrome. Unfortunately, there are no generally accepted criteria for cytokine release syndrome. According to Russian clinical guidelines [19], the indication for prescribing anticytokine drugs in COVID-19 was C-reactive protein (CRP) level above 60 mg/L. Thus, the criteria for inclusion in the study were: age over 18 years; laboratory-confirmed COVID-19 (a positive result of PCR on nasopharyngeal swab) or suspected COVID-19 (based on the complex of clinical, radiological and epidemiological data) [18, 19]; the absence of pregnancy; the signing of informed consent to the administration of drugs off-label; CRP level above 60 mg/L. Patients used other anticytokine drugs (except tocilizumab and sarilumab) were excluded.

To patients in the test group (SAR group), sarilumab was administered subcutaneously at a single dose of 200 mg.

There were two control groups. The first group consisted of patients who were administered tocilizumab once intravenously at a dose of 8 mg/kg (TOC group). The second group included patients who did not receive anticytokine treatment (CON group) (Table 1, Figure 1).

The choice of the anticytokine drugs was determined by their availability in the Clinic. If these drugs were not available, anticytokine treatment was not performed and this patient was included in the control group without anticytokine treatment (CON group).

Patients in all the groups also received antiviral, antibacterial, anticoagulant, and dexamethasone treatment according to indications and contraindications (Table 2).

Survival or death of the patient was considered as the final outcome.

Duration of hospitalization, total duration of the disease, the incidence of admission to intensive care unit and mechanical ventilation, the change in the values of key biomarkers and respiratory function in 7–10 days after administration of anticytokine drug were considered as additional outcomes. The main side effects (cytopenia,

Table 1. Basic characteristics of patients included in the study
Таблица 1. Основные характеристики пациентов, включенных в исследование

Patients' characteristics ***Характеристика пациентов***	**SAR group** ***Группа*** **«SAR» (*n* = 24)**	**TOC group** ***Группа*** **«TOC» (*n* = 27)**	**CON group** ***Группа*** **«CON» (*n* = 47)**	***p***		
				«SAR» vs. «TOC»	**«SAR» vs. «CON»**	**«TOC» vs. «CON»**
Age, years *Возраст, лет*	59 [53–66]	59 [45–66]	62 [54–70]	0.842	0.540	0.100
Male / Female, *n* *Мужчины / Женщины, n*	14 / 10	14 / 13	23 / 24	0.642	0.453	0.809
Body temperature at admission, °C *Температура тела при поступлении, °C*	38.0 [37.4–38.2]	38.0 [37.5–38.5]	37.8 [37.4–38.3]	0.617	0.130	0.152
Body mass index, kg/m^2 *Индекс массы тела, кг/м^2*	33.4 [29.4–34.7]	30.5 [24.9–32.7]	30.0 [26.4–33.3]	0.229	0.236	0.824
Hospital stay, days *Длительность госпитализации, дни*	17 [14–21]	20 [17–25]	16 [13–21]	0.154	0.492	0.019
Total duration of disease, days *Общая длительность заболевания, дни*	25 [22–29]	27 [22–31]	23 [20–29]	0.385	0.470	0.081
Death, *n* *Смерть, n*	3 (12.5 %)	4 (14.8 %)	15 (31.9 %)	0.389	0.021	0.039
Admission to ICU, *n* *Госпитализация в ОРИТ, n*	4 (16.7 %)	7 (25.9 %)	22 (46.8 %)	0.422	0.013	0.077
The need for mechanical ventilation, *n* *Потребность в ИВЛ, n*	3 (12.5 %)	6 (22.2 %)	15 (31.9 %)	0.363	0.075	0.373

secondary infections, thrombosis, increased transaminases, cholestasis) were also evaluated.

The value of the main biomarkers of the disease was evaluated at two points: the first point was 1–3 days before the administration of the anticytokine drug, and the second point was 7–10 days after their administration.

After determining the average day of hospitalization when an anticytokine drug was administered, this day of hospitalization ±1 day was used as Point 1 for the group of patients who did not receive anticytokine drugs. The value of biomarkers 7–10 days after this Point 1 was considered as Point 2.

Results are presented as median [interquartile range]. The groups were compared out using Mann — Whitney and Kruskal — Wallis test for continuous data and χ^2 test for categorical data. Wilcoxon test was used to assess the changes in continuous biomarkers. Survival was assessed using the Kaplan — Meier estimator and Cox's F-test. A $p \leq 0.050$ value was taken as the criterion for significance. Statistical calculations were performed using Statistica 10 (TIBCO Software, CA)

Results

The study included 24 patients who received sarilumab (SAR group), 27 patients who received tocilizumab (TOC group) and 47 patients who did not receive anticytokine therapy (CON group) (Fig. 1). There was no significant difference among patient groups in age, gender distribution, body mass index, body temperature at admission, total duration of disease, the incidence of symptoms of COVID-19 and comorbidities, and the frequency of taking other drugs used to treat COVID-19 (Tables 1, 2). Patients who received tocilizumab stayed in hospital longer than those who did not receive anticytokine treatment. Patients who received sarilumab unlike patients

Table 2. Symptoms, comorbidities and used drugs in patients who received sarilumab (SAR group), tocilizumab (TOC group) and who did not receive anticytokine treatment (CON group)

Таблица 2. Симптомы, сопутствующие заболевания и применяемые для лечения коронавирусной инфекции препараты у пациентов, получивших сарилумаб (группа «SAR») или тоцилизумаб (группа «TOC»), а также у пациентов, не получавших антицитокиновой терапии (группа «CON»)

Symptoms, *n* ***Симптомы, n***	**Groups of patients** ***Группы пациентов***			***p***	
	«SAR» (*n* = 24)	**«TOC» (*n* = 27)**	**«CON» (*n* = 47)**	**«SAR» vs. «TOC»**	**«SAR» vs. «CON»**
Fever / *Лихорадка*	23	26	43	0.932	0.499
Cough / *Кашель*	14	18	29	0.539	0.784
Runny nose / *Насморк*	0	2	1	0.174	0.472
Sore throat / *Боль в горле*	0	1	0	0.341	–
Chest pain / *Боль в груди*	3	1	1	0.244	0.073
Dyspnea / *Одышка*	16	15	24	0.417	0.21
Headache / *Головная боль*	3	4	10	0.811	0.366
Anosmia / *Потеря обоняния*	1	1	0	0.932	0.159
Ageusia / *Потеря вкуса*	1	0	0	0.284	–
Fatigue / *Слабость*	22	26	41	0.483	0.576
Loss of appetite / *Потеря аппетита*	1	1	2	0.932	0.986
Myalgia / *Боль в мышцах*	1	0	1	0.284	0.623
Arthralgia / *Боль в суставах*	0	1	0	0.341	–
Abdominal pain / *Боль в животе*	0	0	0	–	–
Diarrhea / *Диарея*	4	3	6	0.565	0.655
Vomiting / *Рвота*	0	0	0	–	–
Chronic diseases / *Хронические заболевания*					
cardio-vascular system *сердечно-сосудистой системы*	10	17	21	0.128	0.809
respiratory system *дыхательной системы*	3	5	4	0.555	0.594
liver / *печени*	3	3	1	0.878	0.073
kidneys / *почек*	2	1	3	0.483	0.761
rheumatic / *суставов*	0	1	2	0.341	0.305
blood / *системы крови*	1	0	0	0.284	0.159
cancer / *онкологические*	1	1	2	0.932	0.986
diabetes mellitus / *сахарный диабет*	7	9	7	0.749	0.153
Drugs / *Препараты*					
dexamethasone / *дексаметазон*	23	24	43	0.357	0.499
azithromycin / *азитромицин*	14	17	35	0.735	0.164
moxifloxacin / *моксифлоксацин*	6	3	9	0.194	0.568
levofloxacin / *левофлоксацин*	6	13	16	0.088	0.436
amoxicillin/clavulanate *амоксициллин/клавулонат*	3	4	5	0.811	0.815
meropenem / *меропенем*	5	11	10	0.126	0.966
ceftriaxone / *цефтриаксон*	11	16	24	0.338	0.677
clarithromycin / *кларитромицин*	0	1	1	0.341	0.472
hydroxychloroquine *гидроксихлорохин*	19	20	30	0.669	0.186
enoxaparin / *эноксопарин*	21	25	39	0.542	0.619

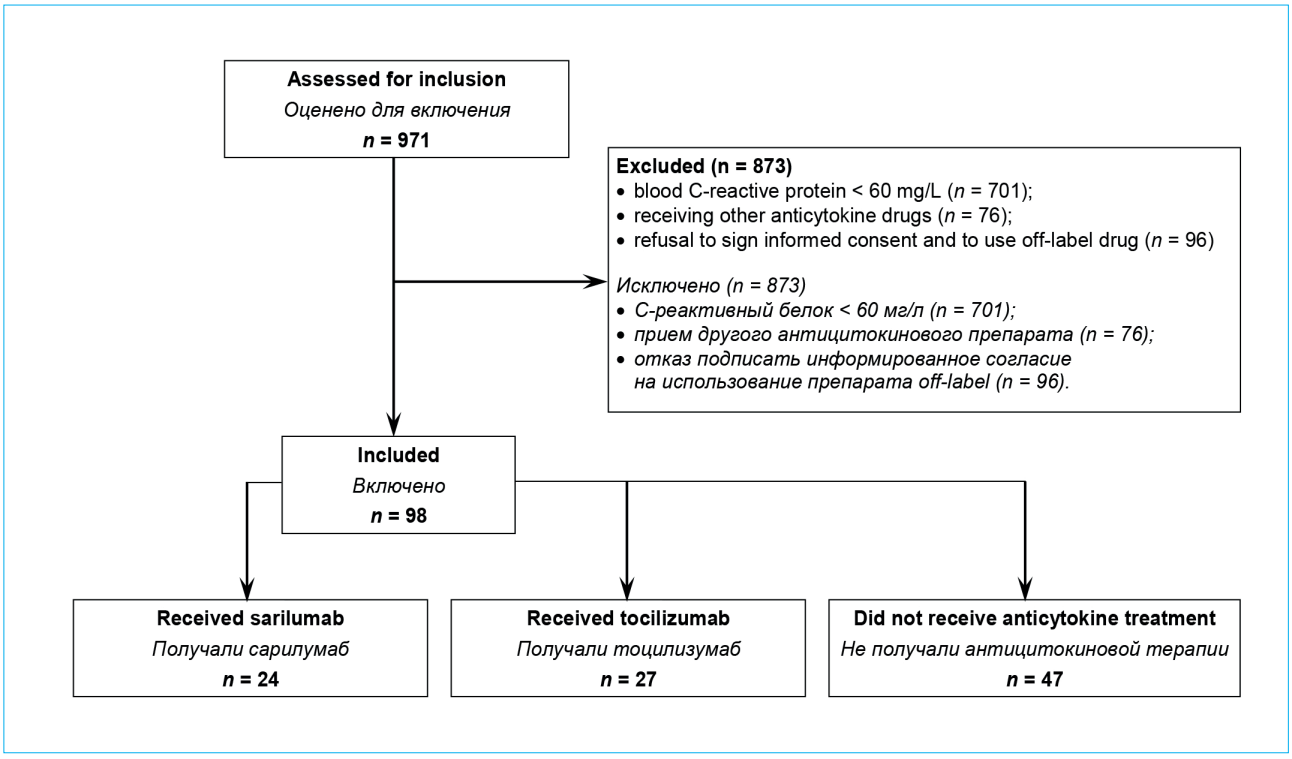

Figure 1. Flow chart for dividing patients included in the study into groups

Рисунок 1. Блок-схема разделения пациентов, включенных в исследование, по группам

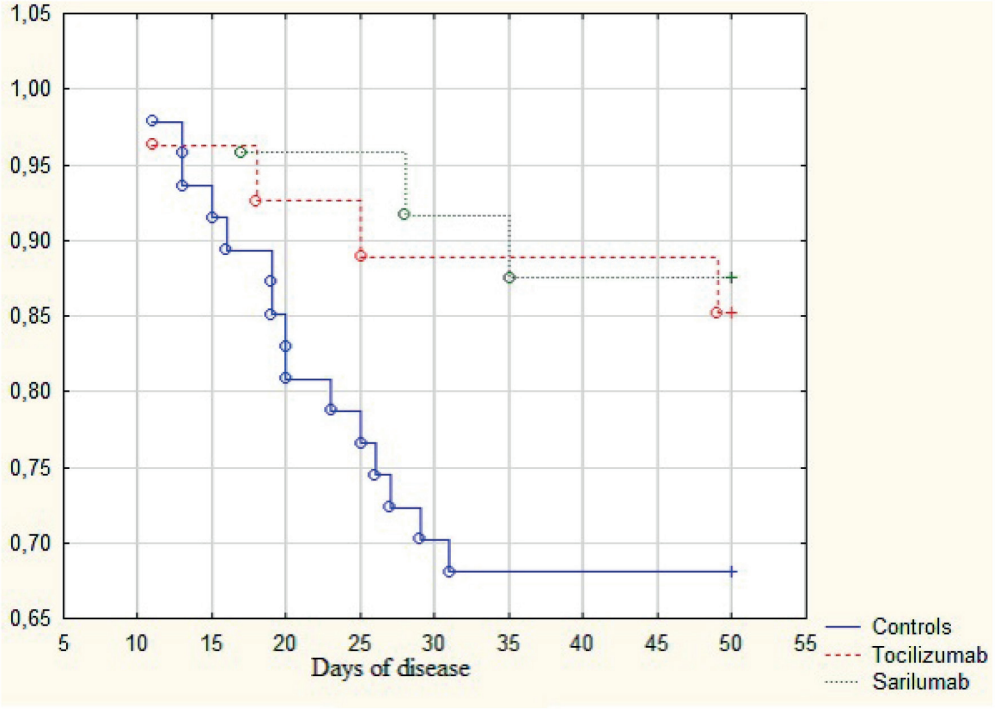

Figure 2. Survival curves for patients with COVID-19 and cytokine release syndrome who did not receive anticytokine treatment («Controls»), received tocilizumab («Tocilizumab») and sarilumab («Sarilumab»)

Рисунок 2. Кривая выживаемости пациентов с COVID-19 и синдромом высвобождения цитокинов, которые не получали антицитокиновой терапии (Controls), получали тоцилизумаб или сарилумаб

who received tocilizumab were less likely to require intensive care unit admission than patients who did not receive anticytokine drugs. The difference between groups in patients' need for mechanical ventilation did not reach the limits of significance (Table 1).

Patients who received tocilizumab or sarilumab had better survival rates than those who did not receive anticytokine treatment (85.2 and 87.5 % vs. 68.1 %; $p = 0.021$ and $p = 0.039$). There was no significant difference in mortality between the groups of patients treated with tocilizumab and sarilumab ($p = 0.389$) (Fig. 2).

Cox regression showed that taking sarilumab was an independent favorable prognostic factor (hazard ratio (HR) — 0.27; 95 % confidence interval (CI): 0.07–0.97), but diabetes mellitus (HR = 4.29; 95 % CI: 1.56–11.90) and the age over 60 years (HR = 5.32; 95 % CI: 1.13–25.10) were independent poor prognostic factors.

There was no significant difference between patient groups in the value of most biomarkers tested before anticytokine drug administration (Table 3). There was a significant decrease in the activity of lactate dehydrogenase only in the group of patients received sarilumab. A significant increase in oxygen saturation was observed only in the groups of patients receiving anticytokine drugs and this increase was higher in the group of patients receiving sarilumab. A significant decrease in body temperature, CRP and fibrinogen level, and an increase in alanine aminotransferase activity, lymphocyte and platelet count were in all groups of patients. However, the decrease in CRP levels in the groups with anticytokine drugs was significantly greater than in the group in which they were not used without a significant difference between SAR and TOC groups. The maximum decrease in fibrinogen level was observed in the group of patients receiving tocilizumab, and the maximum increase in oxygen saturation and lymphocyte count was in the group of patients receiving sarilumab. There was no significant difference between the groups of patients in body temperature, white blood cell, neutrophil and platelet count, creatinine and D-dimer level and transferase activity 7–10 days after administration of anticytokine drugs (Table 3).

In 7–10 days after anticytokine drug administration, half of patients no longer needed respiratory support (the O_2-mask) in the group of patients received sarilumab. There were no significant changes in the group of patients received tocilizumab. In the group of patients who did not receive anticytokine drugs, multidirectional changes were observed: 23.4 % of patients required mechanical ventilation, 19.1 % of patients no longer needed respiratory support, and the others remained without significant changes (Table 3).

Seven-ten days after the administration of the anticytokine drug, the number of patients who needed to be in a prone position significantly increased among patients who did not receive anticytokine treatment, and did not significantly change in the groups of patients received anticytokine drugs (Table 3).

In patients who received anticytokine treatment, injection reactions and the development of cytopenias were not observed. There was no significant difference between patient groups in the frequency of detection of signs of pulmonary embolism, hepatotoxicity, and acute kidney injury after administration of these drugs. Uncomplicated urinary infection was more common in patients received sarilumab (Table 4).

Discussion

Treatment of severe COVID-19 remains a medical challenge. One of the factors determining mortality in COVID-19 is the development of cytokine release syndrome [1–3]. Despite the negative conclusions of the first RCTs [20, 21], a series of meta-analyzes of the results of these and subsequent studies have shown that tocilizumab is effective in the treatment of this disease [7–11].

Unlike tocilizumab, sarilumab has been studied much less in COVID-19. Despite encouraging results from uncontrolled studies [13–15], a large RCT has not shown its significant effect in COVID-19 [16]. However, as it was noted in the Introduction section, this may be due to the fact that the inclusion criteria in that study was the need for supplemental oxygen or mechanical ventilation, while the point of action of this drug is a cytokine storm. This may be the reason for the negative result of that trial. The median CRP value in that study was 1.5 times lower than that in ours. In addition, it should be noted that the first RCTs investigating the effect of tocilizumab in COVID-19 also showed a negative result [20, 21], despite the positive conclusion of subsequent meta-analyzes [7–11]. Results from other RCTs should be awaited, especially those that used cytokine release syndrome rather than respiratory failure as inclusion criteria.

Unfortunately, there is no generally accepted criterion for the development of cytokine release syndrome. Perhaps the ideal of these would be the level of pro-inflammatory cytokines, in particular IL-6, but these tests are expensive and are not yet available in most clinics. We used CRP as a biomarker for the development of this syndrome, because it is the main biomarker of inflammation

Table 3. Change in the values of the main biomarkers 7–10 days after the administration of anticytokine drugs
Таблица 3. Изменения в значениях основных биомаркеров в течение 7–10 дней после приема антицитокиновых препаратов

Parameter / *Параметр*	SAR (*n* = 24)			TOC (*n* = 27)			CON (*n* = 47)			*p****	*p*		
											SAR vs. TOC	SAR vs. CON	TOC vs. CON
	Point 1 *Точка 1*	Point 2 *Точка 2*	*p***	Point 1 *Точка 1*	Point 2 *Точка 2*	*p***	Point 1 *Точка 1*	Point 2 *Точка 2*	*p***	Point 1 *Точка 1*	Point 2 *Точка 2* ****	Point 2 *Точка 2* ****	Point 2 *Точка 2* ****
Lung lesion volume, % *Объем пораженной легочной ткани, %*	46 [38–50]	38 [31–50]	0.146	50 [44–63]	50 [38–63]	0.641	44 [35–63]	38 [28–61]	0.056	0.351	0.039	0.942	0.031
C-reactive protein, mg/L *С-реактивный белок, мг/л*	184 [134–237]	5 [3–10]	<0.001	146 [93–214]	3 [2–9]	<0.001	138 [103–169]	14 [4–49]	<0.001	0.082	0.236	0.016	<0.001
Oxygen saturation, % *Насыщение крови кислородом, %*	88 [85–93]	96 [93–97]	0.001	90 [82–92]	92 [85–95]	0.004	91 [85–94]	94 [74–97]	0.764	0.198	0.022	0.241	0.563
Body temperature, °C *Температура тела, °C*	37.8 [37.1–38.3]	36.6 [36.4–36.6]	<0.001	37.4 [36.7–37.8]	36.6 [36.5–36.8]	<0.001	37.5 [36.7–38.0]	36.6 [36.4–36.7]	<0.001	0.372	0.126	0.557	0.305
Fibrinogen, g/L *Фибриноген, г/л*	7.0 [6.3–9.1]	3.8 [3.3–4.3]	<0.001	7.2 [5.6–9.0]	3.0 [2.3–3.7]	<0.001	7.3 [5.6–8.4]	4.4 [3.2–6.0]	<0.001	0.801	0.021	0.120	<0.001
D-dimer, mg/L* *D-димер, мг/л**	0.7 [0.3–3.6]	1.4 [0.4–6.0]	0.925	1.0 [0.6–1.2]	1.4 [1.0–4.7]	0.715	1.0 [0.6–2.4]	1.9 [1.1–2.2]	0.180	0.824	0.954	0.786	0.710
White blood cells, $\times 10^9$/L *Лейкоциты, 10^9/л*	8.1 [6.8–10.4]	9.8 [6.9–12.5]	0.153	7.8 [4.9–12.0]	8.9 [6.4–12.6]	0.381	7.0 [5.6–8.4]	11.1 [7.0–14.1]	<0.001	0.392	0.623	0.508	0.293
Neutrophils, $\times 10^9$/L *Нейтрофилы, 10^9/л*	6.0 [4.2–7.6]	6.7 [3.9–8.6]	0.838	6.6 [4.8–9.1]	5.9 [4.5–10.3]	0.866	5.5 [4.2–8.0]	7.7 [4.2–11.8]	0.001	0.739	0.807	0.232	0.391
Lymphocytes, $\times 10^9$/L *Лейкоциты, 10^9/л*	0.9 [0.6–1.3]	1.6 [1.3–2.2]	0.025	0.9 [0.6–1.2]	1.2 [0.7–1.8]	0.032	0.8 [0.6–1.1]	1.4 [0.7–2.0]	<0.001	0.725	0.026	0.188	0.400
Platelets, $\times 10^9$/L *Тромбоциты, 10^9/л*	224 [173–311]	304 [249–428]	0.008	195 [174–267]	273 [207–364]	0.012	230 [189–268]	283 [206–439]	0.005	0.787	0.066	0.279	0.451
Creatinine, umol/L *Креатинин, мкмоль/л*	95 [90–103]	86 [78–99]	0.066	88 [77–104]	85 [70–91]	0.026	87 [81–108]	82 [71–97]	0.009	0.168	0.214	0.346	0.657
ALT, U/L *АЛТ, МЕ/л*	48 [28–60]	66 [54–122]	0.024	31 [25–44]	71 [39–136]	<0.001	36 [24–60]	56 [34–84]	0.014	0.282	0.961	0.058	0.054
AST, U/L *АСТ, МЕ/л*	42 [31–53]	31 [21–45]	0.066	39 [26–54]	35 [24–48]	0.563	46 [29–71]	56 [34–84]	0.001	0.274	0.466	0.397	0.827
LDH, U/L *ЛДГ, МЕ/л*	638 [487–854]	521 [434–745]	0.037	779 [539–939]	633 [518–1020]	0.426	673 [500–907]	492 [354–868]	0.081	0.336	0.043	0.750	0.052

Continuation of Table 3. Change in the values of the main biomarkers 7–10 days after the administration of anticytokine drugs
Продолжение таблицы 3. Изменения в значениях основных биомаркеров в течение 7–10 дней после приема антицитокиновых препаратов

Interleukin-6, pg/mL* *Интерлейкин-6, пг/мл**| 65 [36–122]	19 [18–25]	0.500	70 [41–111]	81 [47–148]	0.953	–	–	–	0.723	0.351	–	–
Supplemental oxygen, *n* *Кислородная поддержка без ИВЛ, n*	21 (87.5 %)	9 (37.5 %)	0.001	18 (66.7 %)	16 (59.3 %)	0.573	33 (70.2 %)	13 (27.7 %)	<0.001		0.121	0.396	0.007
Mechanical ventilation, *n* *ИВЛ, n*	0 (0.0 %)	0 (0.0 %)	–	0 (0.0 %)	3 (11.1 %)	0.075	0 (0.0 %)	11 (23.4 %)	<0.001	0.190	0.093	0.010	0.194
No respiratory support, *n* *Самостоятельное дыхание без кислородной поддержки, n*	3 (12.5 %)	15 (62.5 %)	0.001	9 (33.3 %)	8 (29.6 %)	0.770	14 (29.8 %)	23 (48.9 %)	0.057		0.019	0.278	0.105
Prone position, *n* *Прон-позиция, n*	4 (16.7 %)	3 (12.5 %)	0.683	5 (18.5 %)	3 (11.1 %)	0.444	5 (10.6 %)	14 (29.8 %)	0.021	0.602	0.878	0.106	0.066

Note: SAR – group of patients treated with sarilumab; TOC – group of patients treated with tocilizumab; CON – group of patients who did not receive anticytokine drugs; Point 1 – 1–3 days before taking anticytokine drugs or equivalent days in the CON group; Point 2 – 7–10 days after taking anticytokine drugs or equivalent days in the CON group; * – interleukin-6 and D-dimer were not studied in all patients; ** – difference between points 1 and 2; *** – difference between all groups at point 1; **** – the difference between certain groups at point 2.
Примечание: SAR – группа пациентов, получавших сарилумаб; TOC – группа пациентов, получавших тоцилизумаб; CON – группа пациентов, не получавших антицитокиновых препаратов; Точка 1 – 1–3 дня до приема антицитокиновых препаратов или эквивалентные дни в группе CON; Точка 2 – 7–10 дней после приема антицитокиновых препаратов или эквивалентные дни в группе CON; * – интерлейкин-6 и D-димер были исследованы не у всех пациентов; ** – разница между точками 1 и 2; *** – разница между всеми группами в точке 1; **** – разница между определенными группами в точке 2.

and can be easily determined in all clinics of the world.

Mortality in the sarilumab group was also lower than in the control group and did not differ from mortality in the tocilizumab group in our study.

Tocilizumab and sarilumab showed the same effect in reducing level of the main inflammatory marker CRP.

Respiratory function changed differently in different groups during the first week after the administration of the anticytokine drug. The divergent changes was observed in the group that did not receive anticytokine drugs: respiratory function improved in a quarter of patients and they no longer needed for supplemental oxygen, and, on the contrary, it worsened in an other quarter: they began to need for mechanical ventilation and a transfer to a prone position. Stabilization of the respiratory function was in most patients received tocilizumab. While in the sarilumab group, there was mainly an improvement in respiratory function, which was manifested by an increase in the proportion of patients who did not need for supplemental oxygen.

The use of sarilumab and tocilizumab was not accompanied by the development of post-injection reactions and significant side effects. An increase in the proportion of patients with uncomplicated urinary infections in the sarilumab group did not have a significant effect on the course of their diseases. Perhaps the absence of the development of such complications characteristic of these drugs as secondary infections and cytopenias may be explained by the concomitant intake of antibacterial drugs and glucocorticoids, which stimulate hematopoiesis, preventing the development of cytopenias.

The strengths of our work are that this is the first study in which effect of sarilumab in COVID-19 has been compared with that of significantly more studied tocilizumab.

The limitation of our study is its retrospective and non-randomized nature. Although, the study groups did not differ in the base line parameters, selection biases cannot be excluded.

Conclusion

In conclusion, our study showed that sarilumab is at least as good as, and at most superior, tocilizumab in the treatment of cytokine release syndrome in COVID-19. A prospective randomized trial is needed to verify our results.

Table 4. Complications of COVID-19 and adverse events of its treatment in patients who received sarilumab, tocilizumab and did not receive anticytokine drugs (number of persons)

Таблица 4. Осложнения COVID-19 и нежелательные последствия его лечения у пациентов, получивших сарилумаб, тоцилизумаб и не получавших антицитокиновой терапии (количество человек)

Complications *Осложнения*	Groups of patients *Группы пациентов*			*p*		
	SAR *n* = 24	TOC *n* = 27	CON *n* = 47	SAR vs. TOC	SAR vs. CON	TOC vs. CON
Pulmonary embolism *Тромбоэмболия легочной артерии*	2 (8.3 %)	3 (11.1 %)	8 (17.0 %)	0.739	0.320	0.492
Acute kidney injury *Острое повреждение почек*	3 (12.5 %)	4 (14.8 %)	3 (6.4 %)	0.811	0.381	0.233
Extrapulmonary infections *Внелегочные инфекции*	4 (16.7 %)**	2 (7.4 %)**	0 (0.0 %)	0.306	0.004	0.059
ALT > ULN *АЛТ > ВГН*	20 (83.3 %)	16 (59.3 %)	31 (66.0 %)	0.060	0.124	0.649
ALT > 3 ULN *АЛТ > 3 ВГН*	8 (33.3 %)	10 (37.0 %)	12 (25.5 %)	0.782	0.489	0.298
ALT > 3 ULN *АЛТ > 10 ВГН*	3 (12.5 %)	2 (7.4 %)	6 (12.8 %)	0.542	0.975	0.474
Laboratory signs of cholestasis* *Лабораторные признаки холестаза**	0 (0.0 %)	1 (3.7 %)	0 (0.0 %)	0.341	–	0.192

Note: ULN — upper limit of normal; * — increase in the activity of gamma-glutamyltransferase and alkaline phosphatase above ULN; ** — uncomplicated urinary infection.

Примечание: ВГН — верхняя граница нормы; * — увеличение активности гамма-глутамилтрансферазы и щелочной фосфатазы выше ВГН; ** — неосложненная мочевая инфекция.

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