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Risk of secondary bacterial infections during treatment with anti-inflammatory genetically engineered biological drugs in COVID-19 patients

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The aim of the work was to identify the presence and strength of association between the use of anti-inflammatory genetically engineered biological drugs and the development of secondary bacterial infections in COVID-19 patients.
Materials and methods. We used 1 296 medical records of patients hospitalized in the infectious diseases hospital of the Volgograd region with a diagnosis of COVID-19 in September 2020, March and September 2021, March, September and November 2022, have been analyzed. A matched case-control study was performed with 275 pairs identical in gender, age (±2 years), the severity of the lung damage according to computed tomography / chest X-ray, a COVID-19 outcome, concomitant carbohydrate metabolism disorders. Patients with the signs of the secondary bacterial infection (leukocytes ≥12×109/l, procalcitonin ≥0.5 ng/ml and/or viral-bacterial pneumonia according to the autopsy data) were presented as a case. The "control" group included patients without signs of any bacterial infection (leukocytes <11×109/l, procalcitonin <0.5 ng/ml, no description of clinical signs of the bacterial infection in the medical record during the hospitalization). The prescription of 6 anti-inflammatory genetically engineered biological drugs (tocilizumab, sarilumab, olokizumab, levilimab, netakimab, secukinumab) has been studied for these groups.
Results. The use of any anti-inflammatory genetically engineered biological drug was associated with the development of the secondary bacterial infection signs (OR=2.41; 95% CI: from 1.54 to 3.77; p <0.001): for levilimab, the OR was 3.44 (95% CI: from 1.64 to 7.23; p <0.001), for tocilizumab – OR=1.75 (95% CI: from 0.73 to 4.17; p=0.201), for olokizumab – OR=1.28 (95% CI: from 0.81 to 2.03; p=0.292).
Conclusion. Among the three drugs (tocilizumab, olokizumab, levilimab), the Russian biosimilar olokizumab, a monoclonal antibody to circulating interleukin-6, has shown itself as the safest drug in terms of preventing the secondary bacterial infection signs. Further studies of developing bacterial complications risk in COVID-19 patients receiving anti-inflammatory genetically engineered biological drugs are required.
Keywords: genetically engineered biological drugs; interleukin antagonists; COVID-19; tocilizumab; olokizumab; levilimab; case-control study
Abbreviations: FO – fatal outcome; SBI – secondary bacterial infection; GEBDs – genetically engineered biological drugs; ARDS – acute respiratory distress syndrome; CRP – C-reactive protein; OR – odds ratio; CI – confidence interval; CT – computed tomography; XR – X-ray.

Оценка риска возникновения вторичных бактериальных инфекций у больных COVID-19 при приёме противовоспалительных генно-инженерных биологических препаратов

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Цель. Выявить наличие и степень выраженности связи между применением противовоспалительных генно-инженерных биологических препаратов и развитием вторичных бактериальных инфекций у больных COVID-19.

Материалы и методы. Проанализировано 1296 медицинских карт пациентов, госпитализированных с диагнозом COVID-19 в сентябре 2020 года, марте, сентябре 2021 года, марте, сентябре и ноябре 2022 г. Выполнено исследование «случай-контроль» с использованием метода подбора пар «matched case-control study» (275 пар), идентичных по полу, возрасту (±2 года), степени тяжести поражения лёгких по данным компьютерной томографии / рентгенографии лёгких, исходу COVID-19, сопутствующими нарушениями углеводного обмена. В качестве «случая» были представлены пациенты с признаками вторичной бактериальной инфекции (по показателям: лейкоциты ≥12×109/л, прокальцитонин ≥0,5 нг/мл и/или вирусно-бактериальная пневмония по данным аутопсии). В качестве «контроля» были пациенты без признаков бактериальной инфекции (лейкоциты <11×10^9/л, прокальцитонин <0,5 нг/мл, отсутствие описания клинических признаков бактериальной инфекции в медицинской карте на протяжении всей госпитализации). Для указанных групп исследовали назначения 6 противовоспалительных генно-инженерных биологических препаратов (ГИБП): тоцилизумаб, сарилумаб, олокизумаб, левилимаб, нетакимаб, секукинумаб.

Результаты. Применение любого противоспалительного ГИБП было ассоциировано с появлением признаков вторичной бактериальной инфекции (ОШ=2,41; 95% ДИ от 1,54 до 3,77; *p* <0,001): для левилимаба ОШ составило 3,44 (95% ДИ от 1,64 до 7,23; *p* <0,001), для тоцилизумаба – ОШ=1,75 (95% ДИ от 0,73 до 4,17; *p*=0,201), для олокизумаба – ОШ=1,28 (95% ДИ от 0,81 до 2,03; *p*=0,292).

Заключение. Среди трёх препаратов (тоцилизумаб, олокизумаб, левилимаб) наибольшей безопасностью в отношении предупреждения признаков вторичной бактериальной инфекции был препарат олокизумаб. Стоит отметить, что требуется дальнейшее изучение риска развития бактериальных осложнений у пациентов с COVID-19 на фоне применения противовоспалительных ГИБП.

Ключевые слова: генно-инженерные биологические препараты; антагонисты интерлейкинов; COVID-19; тоцилизумаб; олокизумаб; левилимаб; исследование «случай-контроль»

Список сокращений: ЛИ – летальный исход; ВБИ – вторичная бактериальная инфекция; ГИБП – генно-инженерные биологические препараты; ОРДС – острый респираторный дистресс синдром; СРБ – С-реактивный белок; ОШ – отношение шансов; ДИ – доверительный интервал; КТ – компьютерная томография; РГ – рентгенография.

INTRODUCTION

A variety of respiratory viruses often infect people during their lifetime and may lead to bacterial superinfections. Until recently, the influenza A virus has been the most dangerous among the causative agents of acute respiratory viral diseases [1]. A retrospective analysis of the preserved histological samples from the 1918 year AH1N1 influenza pandemic led to the conclusion that more than 95% of the fatal cases had been directly associated with secondary bacterial pneumonia [2]. About 70–80% of fatal cases of the 1957–1958 influenza pandemic had been also associated with bacterial pneumonia [3] and 29–55% of patients who died in healthcare facilities from influenza A (H1N1) during the 2009 outbreak, had signs of bacterial infection [4].

At the end of 2019, the first cases of COVID-19 caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in China. At the beginning of the pandemic, the role of bacterial complications of the new infection was raised [5]. B.J. Langford et al. in meta-analysis [6], which covered 3 338 COVID-19 patients in 2020, studied the prevalence of the bacterial infection of the respiratory tract and/or bloodstream in patients with a confirmed COVID-19 diagnosis. Bacterial co-infections (less than 2 days from the admission to hospital) were detected in 3.5% of COVID-19 patients, and secondary bacterial infections (SBI; more than 2 days from the admission to hospital) were detected in 14.3% of patients. More than 70% of patients hospitalized with COVID-19 in 2020, received antibiotics [6].

W.H. Chong et al, in a meta-analysis of 2021 [7] examined the prevalence of secondary bacterial and fungal kinds of infection in hospitalized COVID-19 patients. The incidence of the secondary bacterial pulmonary infection in the hospitalized was 16% (580 cases out of 3 633 patients). Only 9 of 49 included studies had microbiology data. The most common bacterial agents identified in the respiratory tract sample cultures in the nine observational studies reporting the type and incidence of the SBI, were *Pseudomonas aeruginosa*, *Klebsiella species*, *Staphylococcus aureus*, *Escherichia coli*, and *Stenotrophomonas maltophilia*. According to the studies, 60 to 100% of patients received antibacterial drugs [7].

According to J.M. Farrell et al, the true prevalence of the bacterial concomitant and SBI in COVID-19 patients may be higher because of the difficulties that arise in the differential diagnosis of viral and bacterial pneumonia in

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real clinical practice, as well as the difficulties in collecting respiratory samples from patients in quarantine [3].

As with influenza, SBIs may affect the prognosis of COVID-19 patients. In a retrospective cohort study including patients in Wuhan, China, F. Zhou et al. [8] found that bacterial infections (bacteremia and pneumonia) were more common in fatal COVID-19 cases compared with recovered patients: 28/191 (15%) patients had a culture-positive bacterial infection, and all of these patients except one died. Half of the fatal cases patients (27/54) had a bacterial co-infection, while only 1 case (1/137) of the recovered patients had a bacterial co-infection [8]. Similar patterns of a high incidence of bacterial infections among the deceased patients have been reported in more recent studies [9, 10].

Recent studies have shown that an excessive interferon production and an uncontrolled inflammation are the main mechanisms which contribute to the development of bacterial infections, regardless of the type of a respiratory virus [1]. Compared to normal mice, the genetically modified mice deficient in type I interferon receptors, are more resistant to the development of an acute respiratory distress syndrome, bacterial pneumonia, or sepsis [11–13]. Thus, reducing the risk of development and severity of a cytokine storm, a characteristic complication of a new infection, may lead to a reduced risk of not only ARDS but also of a bacterial superinfection. However, anti-inflammatory genetically engineered biological drugs (GEBDs) such as tocilizumab, sarilumab, and others, used to prevent and treat a cytokine storm in COVID-19, can cause infectious complications due to the immunosuppression.

In patients with rheumatoid arthritis, the most common adverse reactions to tocilizumab in preclinincal and clinical trials were upper respiratory tract infections [14–16]. The rate of serious infections during therapy with another interleukin-6 antagonist, sarilumab, in one study in patients with rheumatoid arthritis, was the same as the similar rate during the therapy with tocilizumab, which makes it possible to conclude that this adverse reaction is class specific [17].

A.I. Rutherford et al. [18], studied the rate of serious infections among GEBDs to treat rheumatoid arthritis based on the data from the British Society of Rheumatology's Rheumatoid Arthritis Biologicals Registry. 19 282 patients were included in the prospective observational cohort study. The incidence of serious infections was 5.51 cases per 100 patient-years. Compared with the tumor necrosis factor-alpha inhibitor etanercept, tocilizumab had a higher risk of developing serious infections (adds ratio [OR]=1.22; 95% confidence interval [CI] 1.02–1.47). A 30-day mortality rate due to serious infections in patients with rheumatoid arthritis receiving biological therapy was 10.4% (95% CI 9.2–11.6%) [18]. In COVID-19 patients, SBIs may be associated with biologic drug therapy and affect the prognosis of COVID-19 considering the mechanism of the drugs action and the data obtained in patients with rheumatoid arthritis.

THE AIM was to identify the presence and strength of the association between the use of anti-inflammatory biological drugs and the development of secondary bacterial infections in COVID-19 patients to assess the safety of biological therapy.

MATERIALS AND METHODS

Study design

A single-center retrospective observational matched case-control study was conducted. Medical records of the patients hospitalized in the infectious disease departments of City Clinical Hospital No. 3 in Volzhsky, the Volgograd Region (Russia), with a confirmed PCR or a presumptive COVID-19 diagnosis during the periods of maximum hospitalization rate – in September 2020, March, September 2021 and March, September and November 2022 – were selected for the analysis. These patients were to stay in hospital for at least 5 days (1 296 patients). The "cases" were patients with the signs of the bacterial infection (leukocytosis ≥12×109/l with a left shift in the white blood cell count, procalcitonin ≥0.5 ng/mL, and/or a description of viral-bacterial pneumonia according to the autopsy data) appeared more than 48 hours after the admission to hospital. The "controls" were selected if the white blood cell count was <11×109/l, procalcitonin <0.5 ng/mL throughout the hospitalization, and there was no description of clinical signs of a bacterial infection in the medical record. For each patient with the SBI signs (a "case"), a pair was selected in a 1:1 ratio among the patients without bacterial infection signs (a "control"), matching the "case" in terms of gender, age (±2 years), a degree of the lung damage (none / 1–2 / 3–4

degrees according to the computed tomography (CT) or chest X-ray data), the outcome (recovered / died), and the presence / absence of carbohydrate metabolism disorders (Fig. 1). In the presence of several "cases" and/or "controls" matching in all parameters, the pairs were selected using a random number generator.

In medical records of 1 296 patients, 77 had data on possible SBIs in the first 48 h after the hospital admission; 73 had no data to confirm or exclude possible bacterial infections; 245 patients had changes in the blood count during the systemic corticosteroid therapy (leukocytosis 11–12×109/l). The data of these patients were not included in the further analysis (see Fig. 1). 512 patient had SBI signs that appeared 48 h after the hospital admission ("case"): leukocytosis ≥12×109/l, procalcitonin ≥0.5 ng/ml and/or autopsy data (viral-bacterial pneumonia). In 389 patients, the white blood cell count was <11×109/l, procalcitonin <0.5 ng/ml, and there was no description of clinical signs of bacterial infections in the medical record throughout their hospitalization ("control"). 275 pairs were matched for gender (male / female), age (a deviation of ±2 years was allowed to achieve the required sample size), a degree of the lung damage (none / 1–2 / 3–4 degrees according to the CT or chest X-ray), the outcome ("healthy" / "lethal"), and the presence / absence of carbohydrate metabolism disorders from 512 "cases" and 389 "controls". The analysis of prescriptions was performed for all patients in the "case" and "control" groups. The prescription of 6 anti-inflammatory biological drugs was identified: tocilizumab (Roche, Switzerland); sarilumab (Sanofi, France); olokizumab (R-Pharm, Russia); levilimab (Biocad, Russia); netakimab (Biocad, Russia); secukinumab (Novartis, Switzerland). One of the criteria for the use of anti-inflammatory GEBDs was the absence of bacterial infection / sepsis signs in patients before the drug administration, which was confirmed by analyzing the medical records of patients with SBI.

Eligibility criteria

The patients met the following inclusion criteria: the age over 18 years; an informed consent of the patient for the participation in the study and a publication of personal medical information signed on the day of hospitalization; a confirmed COVID-19 diagnosis; an inpatient treatment for at least 5 days; no clinical bacterial infection signs in the first 48 hours of hospital stay. The patients' non-inclusion criteria in the study were clinical signs of a bacterial infection in the first 48 hours of hospital stay (77 patients), no blood count or procalcitonin results on the 5th and subsequent days after the prescribed pharmacotherapy (73 patients). The exclusion criteria from the study were as follows: leukocytosis 11–12×109/l on the 5th and subsequent days after the prescribed pharmacotherapy (245 patients).

Conditions and duration of the study

The study was conducted from January 2022 to May 2024 at the Department of Clinical Pharmacology and Intensive Care of Volgograd State Medical University (Volgograd, Russia).

Ethical approval

The study was performed in accordance with the ethical principles of medical research involving human subjects set out in the WMA Declaration of Helsinki. The study was approved by the Local Ethics Committee of Volgograd State Medical University (Protocol No. 2021/085 dated 24 December 2021). All patients had an informed consent for the use and publication of personal medical information for scientific purposes in their medical records, signed on the day of hospitalization.

Statistical processing

The minimum sample size for the matched case-control study was calculated using an online calculator[1]. A statistical power of 95% for the expected OR of 2.0, an error probability of less than 5.0%, and an expected proportion of the "exposed" individuals among "controls" of 15% (half of the average frequency of the inpatient GEBDs use) was achieved when reaching the sample size of 272 pairs matched 1:1 (544 individuals).

Parametric and nonparametric statistics methods were used using the STATISTICA v10.0 software package (StatSoft Inc., USA), Microsoft Excel 2010 for Windows, and a statistical software for epidemiology developed by

[1] sampsize.sourceforge.net. Available from: http://sampsize.sourceforge.net/iface/s3.html

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the US Centers for Disease Control and Prevention Epi Info™ Version 7.2[2]. Quantitative characteristics (age, bed-days, percentage of the lung damage, laboratory test data) corresponded to the normal distribution according to the Shapiro–Wilk criterion. They were described as the arithmetic mean (M) ± standard deviation (σ), and the statistical significance between the study groups according to these characteristics was tested using the Student's *t*-test. Qualitative characteristics were described using absolute values (*n*) and proportions (%), and the statistical significance between the study groups according to these characteristics was tested using the Pearson's χ^2 criterion. The relationship between the appearance of SBI signs and the use of biological therapy was determined based on OR and a 95% CI. In a case-control study with the use of the matched pair method, the number of pairs in which the risk factor (use of any or a specific biological drug) was present in both the case and the control (case+, control+), the number of pairs in which the risk factor was present only in the case (case+, control-), the number of pairs in which the risk factor was present only in the control (case-, control+), and the number of pairs in which the risk factor was absent (case-, control-) were determined [19]. The significance of the difference between the case and control groups in the matched case-control study was determined using the McNemar test. A difference of $p < 0.05$ was considered statistically significant.

RESULTS

Study participants

Among the patients with SBI signs, the rate of men and individuals with a concomitant hypertension who had suffered a myocardial infarction or stroke, was higher compared to the patients with no signs of infection (Table 1).

Patients with SBI signs had a longer period of hospitalization, a higher rate of the lung damage according to CT and/or X-ray data, and a higher mortality rate (OR for mortality 5.64; 95% CI from 3.54 to 8.98). In the structure of the main drugs used to treat COVID-19, the differences were revealed. Thus, patients with SBI signs received antiviral drugs less often and were prescribed systemic corticosteroids and antibiotics upon admission to hospital more often. No significant differences in the age of patients with and without SBI signs were found (see Table 1). The use of the pair matching method eliminated the differences between the case and control groups in the main matching indicators: gender, a degree of the lung damage and disease outcome, which was accompanied by the elimination of the statistical difference between the groups in comorbidities and the structure of the main drugs used (Table 2). However, the average number of hospital days and the rate of the lung damage were significantly higher in the case group and after pair matching. In patients with signs of nosocomial infections, both initially and after pair matching, the maximum values of leukocyte levels, procalcitonin, and CRP were higher (Tables 1 and 2).

Assessment of the probability of detecting the prescription of anti-inflammatory GEBDs in patients with SBI signs

The prescription of at least one anti-inflammatory biologic drug was found in 38.2% (196/512) of patients who subsequently developed SBI signs (case group) and in 26.2% (102/389) of patients without signs of infection throughout their hospitalization (control group). Fourteen patients in the case group and four patients in the control group received two different anti-inflammatory biologic drugs one by another. Among the anti-inflammatory biologic drugs, olokizumab was most frequently prescribed – 173/316 prescriptions (54.7%), levilimab – 84/316 (26.6%), and tocilizumab – 49/316 (15.5%). 7 patients received Sarilumab, 2 patients – netakimab, and 1 patient – secukinumab (Table 3).

It was possible to match "control" identical in gender, age (±2 years), severity and outcome of COVID-19, the presence or absence of carbohydrate metabolism disorders for 53.7% of "cases" due to the high frequency of SBI signs in the patients hospitalized with COVID-19. The largest number of "cases" for which it was not possible to match a pair were noted among the youngest or the oldest patients. It was not possible to find a pair for patients receiving netakimab and secukinumab, and the frequency of a sarilumab prescription was too low to calculate the OR (Table 4). The probability of detecting the prescription of any anti-inflammatory GEBD and levilimab was significantly higher in patients with SBI signs both in the classic case-control study (Table 3) and in the matched case-control study (Table 4).

[2] Epi Info™. Available from: https://www.cdc.gov/epiinfo/index.html

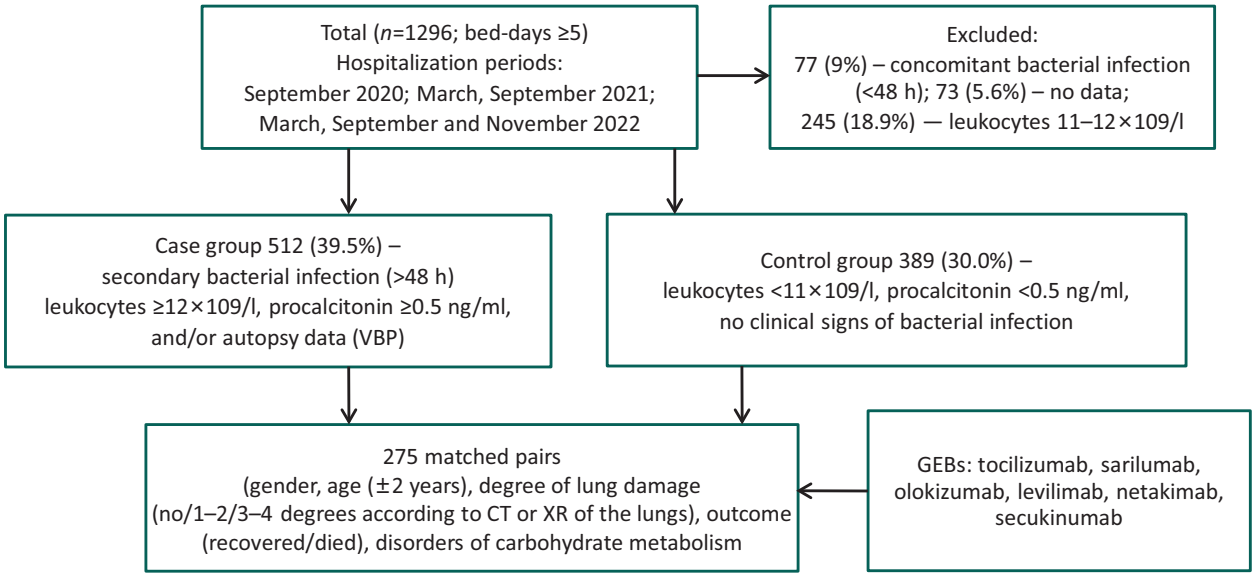

Figure 1 – Study design

Note: VBP – viral-bacterial pneumonia; CT – computed tomography; XR – X-ray; GEBDs – genetically engineered biological drugs.

Table 1 – Initial characteristics of patients

Indicator	"case" (*n*=512)	"control" (*n*=389)	*p*
Signs of bacterial infection	present	absent	
Men / Women, *n* (%)	211/301 (41.2/58.8)	120/269 (30.8/69.2)	**0.002**
Age, years, M±σ	65.5±14.6	64.7±15.9	0.432
Bed-days, M±σ	15.3±7.5	12.1±5.6	**<0.001**
Percentage of lung damage, M±σ	44.8±23.1	29.5±23.5	**<0.001**
Lung damage no / CT(XR)1–2 / CT(XR)3–4, *n* (%)	35/253/224 (6.8/49.4/43.8)	93/224/72 (23.9/57.6/18.5)	**<0.001**
Recovered / died, *n* (%)	378/134 (73.8/26.2)	366/23 (94.1/5.9)	**<0.001**
Hypertension, *n* (%)	366 (71.5)	252 (64.8)	**0.032**
Atrial fibrillation, *n* (%)	74 (14.5)	43 (11.1)	0.133
History of myocardial infarction, *n* (%)	55 (10.7)	25 (6.4)	**0.025**
History of stroke, *n* (%)	22 (4.3)	20 (5.1)	0.552
Disorders of carbohydrate metabolism, *n* (%)	166 (32.4)	114 (29.3)	0.317
White blood cells10^9/l, M±σ	17.0±6.2	8.3±1.8	**<0.001**
Procalcitonin, ng/ml	2.1±8.2	0.2±0.2	**<0.001**
CRP mg/ml, M±σ,	164.2±162.3	76.4±111.8	**<0.001**
Antiviral drugs, *n* (%)	201 (39.3)	220 (56.6)	**<0.001**
Systemic corticosteroids, *n* (%)	478 (93.4)	337 (86.6)	**<0.001**
Anticoagulants, *n* (%)	501 (97.9)	376 (96.7)	0.271
Antibiotics on admission, *n* (%)	307 (59.9)	172 (44.2)	**<0.001**

Note: * – maximum value in the medical record during hospitalization, *p* – Student's *t*-test for quantitative characteristics, Pearson's χ2 test for qualitative characteristics, M – arithmetic mean, σ – standard deviation, CT – computed tomography, chest XR – chest X-ray, CRP – C-reactive protein; *p* <0.05 are highlighted in bold.

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Table 2 – Initial characteristics of patients' matched pairs

Indicator	"case"(*n*=275)	"control" (*n*=275)	*p*
Signs of bacterial infection	present	absent	
Men / Women, *n* (%)	91/184 (33.1/66.9)	91/184 (33.1/66.9)	1.000
Age, years, M±σ	66.3±13.9	66.2±13.9	0.898
Bed-days, M±σ	16.0±7.1	12.4±5.5	**<0.001**
Percentage of lung damage, M±σ	39.1±21.6	35.0±21.9	**0.035**
Lung damage no / CT(XR)1–2 / CT(XR)3–4, *n* (%)	19/184/72 (6.9/66.9/26.2)	19/184/72 (6.9/66.9/26.2)	1.000
Recovered / died, *n* (%)	253/22 (92.0/8.0)	253/22 (92.0/8.0)	1.000
Hypertension, *n* (%)	199 (72.4)	180 (65.5)	0.079
Atrial fibrillation, *n* (%)	37 (13.5)	32 (11.6)	0.520
History of myocardial infarction, *n* (%)	23 (8.4)	20 (7.3)	0.634
History of stroke, *n* (%)	9 (3.3)	17 (6.2)	0.108
Disorders of carbohydrate metabolism, *n* (%)	77 (28.0)	77 (28.0)	1.000
White blood cells10^9/l, M±σ	16.6±5.8	8.4±1.8	**<0.001**
Procalcitonin, ng/ml	1.5±4.9	0.2±0.2	**0.006**
CRP mg/ml, M±σ,	148.3±151.5	82.1±109.6	**<0.001**
Antiviral drugs, *n* (%)	117 (42.5)	138 (50.2)	0.073
Systemic corticosteroids, *n* (%)	257 (93.5)	252 (91.6)	0.417
Anticoagulants, *n* (%)	272 (98.9)	268 (97.6)	0.202
Antibiotics on admission, *n* (%)	142 (51.6)	122 (44.4)	0.088

Note: * – maximum value in the medical record during hospitalization, p – Student's t-test for quantitative characteristics, Pearson's χ2 test for qualitative characteristics, M – arithmetic mean, σ – standard deviation, CT – computed tomography, chest XR – chest X-ray, CRP – C-reactive protein; *p* <0.05 are highlighted in bold.

Table 3 – Probability of detecting the prescription of anti-inflammatory genetically engineered anti-inflammatory drugs in patients with signs of secondary bacterial infection

Risk factor	"case" (*n*=512)		"control" (*n*=389)		OR	95% CI		*p*
	+	–	+	–				
All GEBDs	196	316	102	287	**1.75**	1.31	2.33	**<0.001**
Tocilizumab	33	479	16	373	1.61	0.87	2.96	0.126
Sarilumab	6	506	1	388	4.60	0.55	38.37	0.121
Olokizumab	107	406	66	323	1.29	0.92	1.81	0.142
Levilimab	61	451	23	365	**2.15**	1.30	3.54	**0.002**
Netakimab	2	510	0	389	–	–	–	–
Secukinumab	1	511	0	389	–	–	–	–

Note: Pearson χ^2 p-test, GEBDs – genetically engineered biological drugs, OR – odds ratio, CI – confidence interval, OR and *p* <0.05 are highlighted in bold.

Table 4 – Probability of detecting the prescription of anti-inflammatory genetically engineered anti-inflammatory drugs in patients with signs of secondary bacterial infection in matched pairs

Risk Factor	Number of matched pairs exposed (+) and not exposed (-) to a risk factor				OR	95% CI		*p*
«case»	+	+	–	–				
«control»	+	–	+	–				
All GEBDs	45	65	27	138	**2.41**	1.54	3.77	**<0.001**
Tocilizumab	2	14	8	251	1.75	0.73	4.17	0.201
Sarilumab	0	2	1	272	–	–	–	–
Olokizumab	22	41	32	180	1.28	0.81	2.03	0.292
Levilimab	2	31	9	233	**3.44**	1.64	7.23	**<0.001**

Note: McNemar p-test, GEBDs – genetically engineered biological drugs, OR – odds ratio, CI – confidence interval, OR and *p* <0.05 are highlighted in bold.

DISCUSSION

Despite the fact that COVID-19 is characterized by a lower incidence of bacterial complications compared to the influenza virus, the widespread use of immunosuppressants to treat the cytokine storm is associated with a higher risk of secondary bacterial complications, as shown by the present study and some others [20–22]. In a retrospective single-center cohort study of 2020 [20] with a group selection in a 2:1 ratio (74 patients received tocilizumab, 148 – standard therapy), the use of tocilizumab in patients with a severe and extremely severe COVID-19 was associated with a lower mortality, but with a longer duration of hospitalization. An increase in the duration of hospitalization was associated by R. Rossotti et al., among other things, with the development of infectious complications, which were observed in 32.4% of patients receiving tocilizumab [20]. B. Minihan et al. [21] based on a retrospective analysis of medical records of patients hospitalized with a severe and extremely severe COVID-19, concluded that serious bacterial and fungal infections occurred among 41 patients who had received tocilizumab compared with 33 patients who had received standard therapy (OR=2.67; 95% CI 1.04-6.86; p=0.042). V. Moreno-Torres et al. [22] studied the prevalence and risk factors for bacterial infections in 1594 hospitalized COVID-19 patients. Patients with a bacterial infection (135/1594) were more likely to receive tocilizumab compared with patients without signs of bacterial infection (40 *vs.* 16.9%, p <0.001) [21]. Not all the studies devoted to the investigation of bacterial infections in COVID-19 patients, describe the diagnostic methodology for these complications. However, in the study by V. Moreno-Torres et al. [21], as in the present one, it was indicated that in the individuals for whom bacteriological testing was not possible, the criteria for confirming a bacterial infection were neutrophilic leukocytosis and an increase in procalcitonin levels.

Not all studies have detected a significant association between the use of tocilizumab and bacterial complications. Thus, in a retrospective cohort study with matched groups 1:1 (59 patients received tocilizumab therapy), no reliable differences in the incidence of SBI and fungal infections were found out [23]. In the present study, despite the fact that the rate of the use of any GEBDs was higher in patients with SBI signs for tocilizumab, this was not significant (Tables 3 and 4).

Tocilizumab is the first of the interleukin-6 receptor blocking GEBDs; together with the biosimilar sarilumab, it is included in the international recommendations for the management of COVID-19 patients [24]. Most of the data on the efficacy and safety of anti-inflammatory GEBDs were obtained for tocilizumab [20–24]. In 2020, two biosimilars, olokizumab and levilimab, were approved for use in the Russian Federation and began to be used as an alternative to tocilizumab. These two GEBDs were most frequently used in the hospital under study, but a significant link between the development of SBI and the use of GEBDs was found out for only levilimab. The target of olokizumab is interleukin-6 itself, the excess of which circulates in the blood plasma during the development of a “cytokine storm”, while levilimab, similar to tocilizumab and sarilumab, blocks interleukin-6 receptors on immunocompetent cells. Perhaps the difference in the mechanism of the olokizumab action compared to other anti-cytokine drugs – a blockade of a freely circulating interleukin-6 excess, and not its receptor, on immunocompetent cells, causes a lower incidence of bacterial complications due to the immunosuppressive therapy. This fact requires a further study not only in COVID-19 patients, but also in the patients with rheumatoid arthritis and other systemic inflammatory diseases of the connective tissue.

Study limitations

The main limitation of the present study is common to all case-control analyses compared to randomized controlled trials: although the selection of an appropriate control group seems effective, the possibility of selection bias cannot be completely excluded. The retrospective nature of the study also reduces the reliability of observations, and the detection of SBI is based primarily on clinical data rather than bacteriological examination data. Most patients received empirical antibacterial therapy upon admission to hospital, as a result of which a bacteriological examination was not performed or the results were uninformative, and procalcitonin levels may have been underestimated due to the immunosuppressant therapy, as shown in the study by E.J. Kooistra et al. [25].

CONCLUSION

The use of any anti-inflammatory biological drug was associated with the development of nosocomial infection signs (OR=2.41; 95% CI from 1.54 to 3.77; p <0.001): for levilimab OR=3.44 (95% CI from 1.64 to 7.23; p <0.001), for tocilizumab – OR=1.75 (95% CI from 0.73 to 4.17; p=0.201), for olokizumab – OR=1.28 (95% CI from 0.81 to 2.03; p=0.292). According to the conducted study, among the three drugs (tocilizumab, olokizumab, levilimab), the Russian biosimilar olokizumab has the greatest safety in relation to the development of nosocomial infection signs. Further studies of the risks of developing bacterial complications in COVID-19 patients while using anti-inflammatory GEBDs, are required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Vladimir I. Petrov – study design development, editing and final approval of the article; Anastasia Yu. Ryazanova – data processing, writing the article and final approval of the article; Natalia S. Tokareva – material collection, data processing and final approval of the article. All the authors confirm their authorship compliance with the ICMJE international criteria (all authors made a significant contribution to the conceptualization, research and preparation of the article, read and approved the final version before publication).

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