ISSN 2304-3415, Russian Open Medical Journal
2022. Volume 11. Issue 3 (September). Article CID e0312
DOI: 10.15275/rusomj.2022.0312

Original article

Comparative analysis of immunosuppressive therapy effectiveness in COVID-19 patients

Anton V. Tyurin, Karina E. Akhiyarova, Damir A. Valishin, Lidiya D. Sadretdinova, Leonora N. Khusainova, Naufal S. Zagidullin, Khalida K. Gantseva, Valentin N. Pavlov

Bashkir State Medical University, Ufa, Russia

Received 11 February 2022, Revised 30 March 2022, Accepted 17 May 2022

Abstract: The objective of our study was the analysis of using immunosuppressive therapy in patients with COVID-19 at the Clinic of the Bashkir State Medical University.
Material and methods — We conducted the analysis of clinical and laboratory parameters of inflammatory response in 322 patients with COVID-19 who received tocilizumab, baricitinib, high doses of dexamethasone, or standard therapy.
Results — There was an increase in the levels of leukocytes (p=0.04) and neutrophils (p=0.002) in patients receiving tocilizumab, compared with standard therapy, on days 5 and 10 of a hospital stay. The level of C-reactive protein was initially elevated in all patients, but by day 5 of hospitalization it was significantly higher in patients treated with tocilizumab and baricitinib (p=0.0019 and p=0.013, respectively), compared with high-dose glucocorticoid therapy and standard treatment, against which the normalization of parameter values was noted. The neutrophil-to-lymphocyte ratio increased in the group of patients receiving tocilizumab and high-dose glucocorticoid therapy on day 5 of hospitalization (p=0.017 and p=0.004). When assessing the dynamics of pneumonia, based on computed tomography data, the median of changes exhibited an increase in the volume of lung damage in all groups, compared with the baseline level.
Conclusion — Tocilizumab in the form of monotherapy effectively reduced inflammation, while the efficacy of baricitinib for stopping the cytokine storm in monotherapy was insufficient. Based on CT data, both target drugs did not stop the progression of lung lesions on day 5.

Keywords: COVID-19, SARS-CoV-2, baricitinib, dexamethasone, tocilizumab, immunosuppression.

Cite as Tyurin AV, Akhiyarova KE, Valishin DA, Sadretdinova LD, Khusainova LN, Zagidullin NS, Gantseva KhK, Pavlov VN. Comparative analysis of immunosuppressive therapy effectiveness in COVID-19 patients. *Russian Open Medical Journal* 2022; 11: e0312.

Correspondence to Anton V. Tyurin. Address, Ufa, Russia. Phone: +79273340035. E-mail: anton.bgmu@gmail.com.

Introduction

In 2019, a new species of virus, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), triggering COVID-19 disease, has been detected in Wuhan, China. This virus can cause both mild asymptomatic forms of the disease and severe course, accompanied by the cytokine storm, development of acute respiratory distress syndrome (ARDS), and multiple organ failure [1]. The unfavorable outcome of the COVID-19 disease largely depends on the forcefulness of the immune response, in particular, on excessive release of circulating proinflammatory cytokines: IL-1, IL-2, IL-6, IL-10, TNF-α and interferon gamma (IFN-γ) [2, 3] significantly correlate with the severity of the disease [4], the frequency and degree of lung damage [5], the development of multiple organ failure. Consequently, immunosuppressive therapy is an important part of the pathogenetic therapy of severe forms of COVID-19. At this stage, the main groups of medicamentous drugs are: glucocorticosteroids (GCS) (methylprednisolone, dexamethasone, hydrocortisone), and also targeted therapy: a type of molecular medicine carried out via interfering with the action mechanism of specific (target) molecules by interrupting some metabolic pathway. Since most medicines for targeted therapy are biopharmaceuticals, the term biological (genetically engineered) therapy is sometimes synonymous to targeted therapy. The main representatives of targeted therapy drugs for the cytokine storm are JAK-kinase (aka Janus kinase) inhibitors (baricitinib, tofacitinib), IL-6 inhibitors (tocilizumab, olokizumab, levilimab, sarilumab), and IL1β inhibitors (canakinumab). Published sources describe the results of using these drugs, but they are quite controversial [6, 7, 8].

The objective of this study was to analyze the dynamics of a complete blood count, C-reactive protein level, and CT of the chest organs in various options of immunosuppressive therapy of patients with COVID-19 at the Clinic of Bashkir State Medical University (BSMU).

Material and Methods

Patients

We distributed 332 patients (mean age 57,01±1,6 years) of the COVID hospital at BSMU Clinic between four groups depending on received therapy: Group 1 (receiving high doses of dexamethasone, n=70), Group 2 (receiving tocilizumab, n=13), Group 3 (treated with baricitinib, n=21), and Group 4 including patients undergoing standard therapy (control, n=228). The characteristics of these groups are presented in *Table* 1, along with the results of the analysis of studied parameters in formed groups, compared with the standard therapy group. The exclusion criteria for our study were: history of thrombophlebitis, latent

tuberculosis infection, HBV or HCV infection, current bacterial infection, pregnancy, lactation, intake of oral contraceptives, previous (over the last 5 years) or current malignant neoplasms, neutrophil count <10^9/L, lymphocyte count <0.2×10^9/L, platelet count <50×10^9/L, and transaminase content exceeding fourfold upper normal limit. The study was conducted in compliance with the guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of Bashkir State Medical University (Protocol 11, of 07 November, 2020).

Analysis of clinical parameters

Hematological parameters were analyzed using an automated analyzer, CELL-DYN Sapphire (Abbot, USA). Biochemical parameters were examined using an automated analyzer, CA-800 (Furuno Electric Co. Ltd., Japan). Computed tomography was conducted using Optima CT660 device (General Electric, USA). COVID-19 diagnosis was confirmed by real-time polymerase chain reaction (RT-PCR) (Vector-Best COVID-19 RT-qPCR kit, Russia) of viral nucleic acids from throat swab specimens.

Treatment

All patients received curative treatment with hydroxychloroquine or lopinavir/ritonavir according to the recommended regimens (at the time of treatment, these were Interim Guidelines, "Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)", version 7 of 06.03.2020, Russian Federation), dexamethasone at a dosage of 8 mg/day, anticoagulants and antibiotics according to indications. Tocilizumab dosage was 8 mg/kg intravenously x 1 dose (maximum of 800 mg). Dexamethasone was prescribed at a dose of 20 mg twice a day intravenously for 3 days, then the dose was reduced by 50% every 3 days until complete withdrawal (off-label), and baricitinib was introduced at a dose of 4 mg once a day for 7-14 days. To evaluate the effectiveness of treatment, the following tests were performed: blood test with determination of the number of leukocytes starting on day 1 and then every 5 days, biochemical blood test (C-reactive protein, CRP), CT scan of the chest on days 1 and 5.

Table 1. Characterization of the study groups

	Group 1 (n=70)	*Group 2 (n=13)*	*Group 3 (n=21)*	*Group 4 (n=228)*
Age, years	57.07±2.70 p=0.230	59.1±9.4 p=0.531	59.4±6.6 p=0.336	57.6±1.9
Male, n (%)	29 (42) p=0.514	6 (43) p=0.847	9 (43) p=0.514	103 (45)
Outpatient treatment, days	7.55±0.97 p=0.332	6.1±1.3 p=0.416	6.8±2.3 p=0.811	8.1±1.0
Duration of hospital stay, days	12.67±1.46 p=0.112	16.5±2.6 * p=0.024	18.1±2.25 * p=0.017	11.8±0.5
Artificial lung ventilation, n (%)	4 (5.71) p=0.356	4 (30.77) * p=0.041	2 (9.52) p=0.411	20 (8.77)
Intensive care unit, n (%)	7 (10) p=0.844	4 (30.77) * p=0.029	6 (28.57) * p=0.035	22 (9.65)

* – statistically significant difference yielded by the comparison with Group 4.

Table 2. Results of laboratory tests in the study groups

Parameter	*Day of hospitalization*	*Group 1*	*Group 2*	*Group 3*	*Group 4*
Leukocytes, 10^6/L	1	4.80 [3.40; 6.80], p=0.215	5.39 [3.40; 6.50], p=0.226	4.60 [3.40; 6.60], p=0.451	5.11 [3.80; 7.10]
	5	8.74 [6.75; 13.28], p=0.665	11.30 [7.00; 13.80], p=0.04	8.70 [5.81; 13.70], p=0.298	7.85 [5.85; 9.95]
	10	8.06 [6.55; 12.33], p=0.925	9.50 [7.30; 12.20], p=0.511	9.06 [6.06; 11.63], p=0.322	7.36 [5.70; 10.65]
Neutrophils, %	1	72.10 [58.70; 78.00], p=0.215	63.60 [61.20; 75.70], p=0.502	71.70 [60.30; 82.80], p=0.499	70.90 [61.13; 78.15]
	5	78.05 [68.95; 84.10], p=0.008	83.00 [79.10; 89.20], p=0.002	79.50 [68.20; 85.40], p=0.014	71.75 [60.83; 80.35]
	10	73.60 [60.58; 76.93], p=0.225	83.40 [63.00; 87.20], p=0.622	67.40 [62.00; 78.95], p=0.615	67.10 [58.60; 80.30]
CRP, mg/L	1	32.30 [12.60; 51.40], p=0.537	52.10 [23.50; 68.90], p=0.630	38.80 [15.00; 78.90], p=0.220	26.85 [6.00; 67.95]
	5	5.00 [3.00; 30.00], p=0.250	54.00 [15.10; 70.60], p=0.0019	16.60 [11.60; 52.00], p=0.013	6.00 [3.00; 27.70]
	10	4.00 [2.00; 9.30], p=0.884	10.20 [3.00; 49.8], p=0.174	22.00 [4.00; 71.20], p=0.023	4.00 [1.99; 15.13]
Neutrophil-to-lymphocyte ratio	1	3.22 [1.84; 4.65], p=0.302	2.06 [1.82; 4.35], p=0.911	2.91 [1.82; 6.80], p=0.548	2.92 [1.90; 4.70]
	5	4.89 [3.19; 7.15], p=0.004	5.73 [3.67; 15.37], p=0.017	4.73 [3.43; 7.76], p=0.207	3.44 [1.89; 5.88]
	10	3.76 [2.00; 4.70], p=0.328	6.67; [1.37; 11.13], p=0.281	3.19 [2.25; 4.83], p=0.460	2.66 [1.82; 5.08]
Lymphocyte-to-CRP ratio	1	0.51 [0.26; 0.95], p=0.814	0.69 [0.46; 1.18], p=0.328	0.44 [0.16; 1.25], p=0.544	0.51 [0.25; 1.35]
	5	0.45 [0.14; 0.86], p=0.524	0.25 [0.09; 1.14], p=0.537	0.65 [0.19; 1.83], p=0.297	0.48 [0.16; 1.16]
	10	0.93 [0.10; 1.87], p=0.544	0.11; [0.15; 0.65], p=0.299	0.61 [0.32; 0.83], p=0.805	0.60 [0.20; 1.73]

CRP, C-reactive protein. p-level – statistically significance for difference yielded by the comparison with Group 4.

Table 3. Dynamics of lung damage based on CT data

Study groups	*Deterioration on day 5, n (%)*	*No deterioration on day 5, n (%)*	*Day of hospitalization*	*Lung damage, %*	*P*
Group 1	17 (24.29)	53 (75.71)	1	48.00 [40.00; 60.00]	0.438
			5	48.00 [42.00; 60.00]	
Group 2	6 (46.15)	7 (53.85)	1	52.00 [44.00; 68.00]	0.157
			5	64.00 [55.00; 69.00]	
Group 3	12 (57.14)	9 (42.86)	1	48.00 [40.00; 60.00]	0.030
			5	60.00 [51.00; 68.00]	
Group 4	43 (18.86)	185 (81.14)	1	44.00 [32.00; 56.00]	0.268
			5	48.00 [36.00; 56.00]	

Data processing

Statistical data processing was carried out using Statistica 12 software and Microsoft Excel. The normality of data distribution was examined by using Kolmogorov-Smirnov test. Quantitative data are presented as median with lower and upper quartiles – Me [LQ; UQ]. Intergroup differences were assessed using the Mann-Whitney U test and Fisher's exact test, at a threshold significance level of p=0.05.

Results

In all study groups, a complete blood count and serum C-RP level were identified during hospitalization, on days 5 and 10 of inpatient treatment. The results are presented in *Table* 2.

There were no significant differences in the leukocyte content in all groups after analyzing the level of leukocytes on the first day of hospitalization: their number corresponded to the physiological norm for adults. By day 5 of a hospital stay, there was an increase in the level of leukocytes in patients of Groups 2 and 3 above the reference values; for the tocilizumab group, this increase reached statistical significance, compared with the control group (p=0.04). By day 10 of treatment, normalization of the leukocyte content was confirmed in all groups. The relative number of neutrophils was initially within the reference range in all groups, increasing to the maximum in the tocilizumab group by day 5 (p=0.002).

CRP content was slightly higher in the tocilizumab and baricitinib groups (52.10 mg/L and 38.80 mg/L, correspondingly) versus the control group (26.85 mg/L and dexamethasone (32.30 mg/L), but the differences were not statistically significant. This can be explained by the indications for the appointment of targeted therapy (an initially higher level of CRP). However, on day 5, in the level of CRP was higher Groups 2 and 3 (54.00 mg/L and 16.60 mg/L, respectively) than in the control group (p=0.0019 and p=0.013, correspondingly), and remained such on day 10 of therapy in the baricitinib group (1800, p=0.023), compared with Groups 1 and 4 (4.00 mg/L in each), in which the normalization of this parameter took place already on day 5 of hospitalization. Comparison of the neutrophil-to-lymphocyte and lymphocyte-to-CRP ratios on the first day yielded no differences. On day 5, we observed an increase in the neutrophil-to-lymphocyte ratio in Groups 1 and 2 (6.67, p=0.004 and 5.73, p=0.017), compared with the control group. No intergroup differences in lymphocyte-to-CRP ratio were detected.

When evaluating the dynamics of pneumonia, based on computed tomography, the criterion for the effectiveness of therapy was the absence of an increase in the extent of lung tissue damage. The highest percentage of lung damage on the CT picture was observed in Group 3, acquiring statistical significance (p=0.03), which could be associated with both initially more pronounced inflammation and ongoing therapy. Overall, none of the treatment regimens led to a decrease in the extent of lung damage on day 5 of treatment (*Table* 3).

Discussion

The data on the effectiveness of tocilizumab in the treatment of cytokine storm is conflicting and still being studied. Tocilizumab is a humanized monoclonal antibody that recognizes soluble and membrane-bound forms of the IL-6 receptor. Excessive stimulation of the immune response leads to excessive release of IL-6, responsible for a number of events leading to organ damage and deterioration of the general clinical condition of the patient. IL-6 is a pleiotropic cytokine with several immunological activities. It plays a role in the differentiation of mature B lymphocytes into plasma cells and (in combination with TGF-β) induces the triggers the production of acute phase proteins, such as C-RP, fibrinogen, serum amyloid A, and hepcidin. In the bone marrow, IL-6 stimulates the maturation of megakaryocytes into platelets and the activation of hematopoietic stem cells [9] produced by fibroblasts and activated macrophages, exerting a profibrotic effect in various organs, such as lungs, skin, and liver [10]. Tocilizumab inhibits signaling, mediated by IL-6, causing effective suppression of the immune system [11], which, according to some researchers, reduces the extent of lung damage shown by CT. It also normalizes oxygen saturation level in the blood, CRP, and the number of lymphocytes in the majority of patients [7]. However, some authors ignored the benefits of tocilizumab therapy and provide data on a higher incidence of secondary infection, which complicates the course of viral pneumonia and leads to an increase in a hospital stay duration [12]. In our study, patients treated with tocilizumab experienced a significantly slower decrease in C-RP levels and regeneration of lung tissue damage. The relative number of neutrophils and neutrophil-to-lymphocyte ratio were also elevated, which characterized activity of inflammation and also the extent of lung damage and disease progression in general [13], thereby playing the role of a predictor of an unfavorable outcome [14]. This can be interpreted as a secondary bacterial infection caused by immunosuppression or a possible response to the drug per se.

Of interest is baricitinib, an oral reversible selective JAK1/JAK2 inhibitor. As part of the intracellular signaling pathway, JAK kinases phosphorylate and activate STATs (signal transducers and transcription activators), which in turn activate gene expression in the cell. JAK-STAT is a major cytokine-regulated signaling pathway, critical for triggering innate immunity, driving adaptive immune mechanisms, and limiting inflammatory and immune responses [15]. Via blocking JAK1/JAK2, baricitinib intracellularly suppresses proinflammatory signal of several cytokines, such as IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, and TNF-α [16]. On the one hand, this results in immunosuppression; on the other hand, having an affinity for AAK1 (adapter-associated kinase type 1) or AMP-activating kinase 1 and cyclin-G-associated kinase [17], it inhibits the clathrin-dependent pathway of endocytosis, which prevents the penetration of the virus into cells [18]. Some studies noted a faster elimination of the virus from the patient's body in the baricitinib subjects by taking swabs from the nose and throat, a decrease in the number of transfers to the ICU, and a reduction in the hospital stay duration [19, 20], compared with the control group. Our results implied that monotherapy with baricitinib did not provide a reduction in C-RP level to normal values on day 5 and did not stop the progression of lung damage sensu CT. It is noteworthy that Interim Guidelines, "Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)", version 8 of 09/03/2020 and subsequent versions), baricitinib was excluded as a medication for monotherapy and treatment of severe forms of the disease [21]. Glucocorticosteroids (GCS) are widely used to treat acute and chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, etc. Besides, GCS is frequently prescribed to prevent graft-versus-host immune reaction after organ transplantation, and in some cases – cancer types, such as lymphoma [22]. However, GCS have a number of undesirable side effects, including

impaired glucose tolerance and insulin resistance, osteoporosis, muscle and skin atrophy, arterial hypertension, glaucoma, delayed wound healing, and mental disorders (e.g., insomnia and depression) [23]. Use of corticosteroids in COVID-19 treatment regimens was described with caution: only after the completion of the large controlled British study, RECOVERY, dexamethasone at a dosage of 6 mg per day was included in standard treatment regimens. According to the results of this study, dexamethasone alone significantly reduced mortality in patients with COVID-19, but increased mortality in patients who did not require oxygen therapy and artificial ventilation [24]. This conclusion was supported by a number of authors, especially those focusing on potentially positive effects of dexamethasone on ICU patients and treatment of ARDS [25]. However, in a single-center retrospective study of 256 ICU patients by Monil Majmundar et al., corticosteroid treatment was associated with a significantly lower risk of ICU admission, intubation, or hospital death [26]. Undesirable effects of corticosteroids were also noted, such as decelerating the elimination of the virus [27] and introduction of a secondary infection. According to published sources, corticosteroids could cause neutrophilic leukocytosis [28]. However, in our study, there were no significant differences in the level of leukocytes between the group of patients who received high doses of corticosteroids and the control group.

Conclusion

Hence, the results of our study revealed insufficient effectiveness of baricitinib in monotherapy of patients at the stage of cytokine storm. Medicines in targeted monotherapy did not stop the increase in the percentage of lesions according to lung CT. C-RP is a sensitive marker, along with the neutrophil/lymphocyte ratio, that can be used as an indicator of poor outcome and progression of COVID-19.

Study limitations

The limitations of our study include relatively small sample of patients, lack of long-term control over the state of the studied parameters, and significant differences among study subjects in compiled groups in a number of parameters, such as duration of hospitalization and need of treatment at the intensive care unit.

Funding

The study was carried out within the framework of activities of Eurasian Scientific and Educational Center, and supported by the subsidies in the field of science from the budget of the Republic of Bashkortostan for state support of young scientists – graduate students and PhD degree holders (competition code: SEC-GMU-2021).

Conflict of interest

The authors declare no conflicts of interest.

References

1. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev*. 2020; 53: 38-42. https://doi.org/10.1016/j.cytogfr.2020.04.002.
2. Valencia D. Brief review on COVID-19: The 2020 pandemic caused by SARS-CoV-2. *Cureus* 2020; 12(3): e7386. https://doi.org/10.7759/cureus.7386.
3. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; 395(10223): e30-e31. https://doi.org/10.1016/s0140-6736(20)30304-4.
4. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review. *J Med Virol* 2020; 93(1): 275-299. https://doi.org/10.1002/jmv.26254.
5. Zhang YY, Li BR, Ning BT. The comparative immunological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2 coronavirus infections. *Front Immunol* 2020; 11: 2033 (https://doi.org/10.3389/fimmu.2020.02033.
6. Radbel J, Narayanan N, Bhatt P. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report. *Chest* 2020; 158(1): e15-e19. https://doi.org/10.1016/j.chest.2020.04.024.
7. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. *Clin Immunol* 2020; 214: 108393. https://doi.org/10.1016/j.clim.2020.108393.
8. Praveen D, Puvvada RC, Aanandhi MV. Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19. *Int J Antimicrob Agents* 2020; 55(5): 105967. https://doi.org/10.1016/j.ijantimicag.2020.105967.
9. Picchianti Diamanti A, Rosado M, Pioli C, Sesti G, Laganà B. Cytokine release syndrome in COVID-19 patients, a new scenario for an old concern: The fragile balance between infections and autoimmunity. *Int J Mol Sci* 2020; 21(9): 3330. https://doi.org/10.3390/ijms21093330.
10. Choy E, Rose-John S. Interleukin-6 as a multifunctional regulator: Inflammation, immune response, and fibrosis. Journal of Scleroderma and Related Disorders. 2017; 2(2 Suppl): S1-S5. https://doi.org/10.5301%2Fjsrd.5000265.
11. Pujari R, Thommana M, Ruiz Mercedes B, Serwat A. Therapeutic options for COVID-19: A review. *Cureus* 2020; 12(9): e10480. https://doi.org/10.7759/cureus.10480.
12. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: A single-centre retrospective cohort study. European Journal of Internal Medicine. 2020; 76: 43-49. https://doi.org/10.1016/j.ejim.2020.05.021.
13. Zhang Y, Wu W, Du M, Luo W, Hou W, Shi Y, et al. Neutrophil-to-lymphocyte ratio may replace chest computed tomography to reflect the degree of lung injury in patients with corona virus disease 2019 (COVID-19). *Research Square* 2020; Preprint (Version 1). https://doi.org/10.21203/rs.3.rs-23201/v1.
14. Lagunas-Rangel F. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *J Med Virol* 2020; 92(10): 1733-1734. https://doi.org/10.1002/jmv.25819.
15. Benveniste EN, Liu Y, McFarland BC, Qin H. Involvement of the janus kinase/signal transducer and activator of transcription signaling pathway in multiple sclerosis and the animal model of experimental autoimmune encephalomyelitis. *J Interferon Cytokine Res* 2014; 34(8): 577-588. https://doi.org/10.1089/jir.2014.0012.
16. Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock I. The immune response and immunopathology of COVID-19. *Front Immunol* 2020; 11: 2037. https://doi.org/10.3389/fimmu.2020.02037.
17. Mirzaev KB, Kiselev YuYu, Sychev DA. Methylprednisolone in acute respiratory distress-syndrome in COVID-19: rationales for use, optimal dosage regimens, combined use with tocilizumab. *Good Clinical Practice* 2020; (4S): 23-27. Russian. https://doi.org/10.37489/2588-0519-2020-S4-23-27.
18. Otdelenov VA, Tsvetov VM, Sychev DA. Possibility to use barycytinib in patients with COVID-19, including for treatment of “cytokine storm”.

Good Clinical Practice 2020; (4S): 11-14. Russian. https://doi.org/10.37489/2588-0519-2020-S4-11-14.

19. Cantini F, Niccoli L, Nannini C, Matarrese D, Natale MED, Lotti P, et al. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. *J Infect* 2020; 81(4): 647-679. https://doi.org/10.1016/j.jinf.2020.06.052.
20. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J Infect* 2020; 81(2): 318-356. https://doi.org/10.1016/j.jinf.2020.04.017.
21. Interim Guidelines "Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)". 8th Ed. 2020; 226 p. Russian. https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf.
22. Escoter-Torres L, Caratti G, Mechtidou A, Tuckermann J, Uhlenhaut NH, Vettorazzi S. Fighting the fire: Mechanisms of inflammatory gene regulation by the glucocorticoid receptor. *Front Immunol* 2019; 10: 1859. https://doi.org/10.3389/fimmu.2019.01859.
23. Hartmann K, Koenen M, Schauer S, Wittig-Blaich S, Ahmad M, Baschant U, Tuckermann JP. Molecular actions of glucocorticoids in cartilage and bone during health, disease, and steroid therapy. *Physiol Rev* 2016; 96(2): 409-447. https://doi.org/10.1152/physrev.00011.2015.
24. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; 384(8): 693-704. https://doi.org/10.1056/nejmoa2021436.
25. Bartoletti M, Marconi L, Scudeller L, Pancaldi L, Tedeschi S, Giannella M, et al. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: A multicentre study. *Clin Microbiol Infect* 2021. 27(1): 105-111. https://doi.org/10.1016/j.cmi.2020.09.014.
26. Majmundar M, Kansara T, Lenik JM, Park H, Ghosh K, Doshi R, et al. Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York metropolitan region. *PLoS One* 2020; 15(9): e0238827. https://doi.org/10.1371/journal.pone.0238827.
27. Rafiullah M, Siddiqui K. Corticosteroid use in viral pneumonia: Experience so far and the dexamethasone breakthrough in coronavirus disease-2019. *J Comp Eff Res* 2020; 9(18): 1247-1254. https://doi.org/10.2217/cer-2020-0146.
28. Mareev VY, Orlova YA, Pavlikova EP, Matskeplishvili ST, Krasnova TN, Malahov PS, et al. Steroid pulse-therapy in patients with coronavirus pneumonia (COVID-19), systemic inflammation and risk of venous thrombosis and thromboembolism (Wayfarer Study). *Kardiologiia* 2020; 60(6): 15-29. English, Russian. https://doi.org/10.18087/cardio.2020.6.n1226.

Authors:
Anton V. Tyurin – MD, PhD, Associate Professor, Department of Internal medicine, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0002-0841-3024.
Karina E. Akhiyarova – Instructor, Department of Internal Medicine, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0001-5965-2108.
Damir A. Valishin – MD, DSc, Professor, Chair of the Department of Infectious Diseases, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0002-1811-9320.
Lidiya D. Sadretdinova – Instructor, Department of Internal Medicine, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0001-9421-9545.
Leonora N. Khusainova – MD, PhD, Associate Professor, Department of Internal Medicine, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0002-5590-7270.
Naufal S. Zagidullin – MD, DSc, Professor, Chair of the Department of Propaedeutics of Internal Diseases, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0003-2386-6707.
Khalida K. Gantseva – MD, DSc, Professor, Department of Internal Medicine, Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0002-7217-7222.
Valentin N. Pavlov – MD, DSc, Professor, Academician of Russian Academy of Sciences, Rector of Bashkir State Medical University, Ufa, Russia. http://orcid.org/0000-0003-2125-4897.