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COMPARATIVE ANALYSIS OF DRUG EFFICACY IN THE TREATMENT FOR COVID-19 SEVERE FORMS, BASED ON ATTRIBUTE-BASED STATISTIC METHODS AND ANALYSIS OF DRUG INTERACTIONS

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Severe and critical forms of COVID-19 are beset by the development of “a cytokine storm”, which is characterized by an increased secretion of proinflammatory cytokines. Therefore, one of the leading strategies for treating patients with severe forms of COVID-19 is the reduction of concentration of proinflammatory cytokines and leveling out their effect on the patient. Among the drugs aimed at reducing the concentration of proinflammatory cytokines, IL-6 inhibitors, IL-1 inhibitors, JAK inhibitors and systemic glucocorticosteroids have been found useful in COVID-19. All of these drugs are currently prescribed off-label.

The aim of the work is a comparative analysis of the data from the literature sources in the PubMed system, devoted to the clinical efficacy and safety of IL-6, IL-1, JAK inhibitors and systemic glucocorticosteroids in the treatment for severe forms of COVID-19.

Materials and methods. In the treatment for severe forms of COVID-19, materials for the comparative analysis were the data from the literature sources in the PubMed system, on the studies devoted to the use of the systemic glucocorticosteroid dexamethasone, IL-6 inhibitor tocilizumab, IL-1 inhibitor anakinra, and JAK inhibitor ruxolitinib. The analysis was performed by statistical evaluation of the drugs effect within the 28-day survival rate among the patients with severe COVID-19. Attributive statistics was used as a statistical tool. The safety of the drug use was assessed by analyzing potential drug interactions. The information about potential drug interactions, was obtained from a specialized website – Drugs.com. Knowmore. Besure (https://www.drugs.com/interaction/list/).

Results. As a result of the analysis, it has been established that tocilizumab has the highest efficacy rates. In this respect, it is followed by dexamethasone. The attributive efficacy rates and 95% confidence interval values for the both drugs were statistically significant. The indices of relative and population attributive kinds of efficacy, were also higher for tocilizumab, but a 95% confidence interval of these indices, get into the range of statistically insignificant values, requiring additional evidence of their efficacy. According to the data obtained, tocilizumab efficacy is higher than that of the other drugs compared: NNT (dexamethasone) – 32; NNT (tocilizumab) – 4, NNT (ruxolitinib) – 7; NNT (anakinra) – 35.

Conclusion. The choice of a drug should be based on the patient’s condition, comorbidities, and medications used in therapy to minimize the risk of undesirable drug interactions. Against the background of the lowest efficacy among the compared drugs, a high efficacy for the patients with concomitant hepatobiliary disorders and DIC syndrome, has been established for the inhibitor IL-1 anakinra, which makes it the drug of choice among the patients with these diseases and under these conditions in the development of “a cytokine storm”.

Keywords: severe forms of COVID-19; systemic glucocorticosteroid; IL-6 inhibitor; IL-1 inhibitor; JAK-inhibitor; “cytokine storm”; attributive statistics; drug interactions

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭФФЕКТИВНОСТИ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ В ТЕРАПИИ ТЯЖЕЛЫХ ФОРМ COVID-19 НА ОСНОВАНИИ МЕТОДИК АТРИБУТИВНОЙ СТАТИСТИКИ И АНАЛИЗА МЕЖЛЕКАРСТВЕННЫХ ВЗАИМОДЕЙСТВИЙ

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Тяжелые и критические формы COVID-19 сопровождаются развитием «цитокинового шторма», который характеризуется повышенной секрецией провоспалительных цитокинов. Поэтому одной из ведущих стратегий лечения пациентов с тяжелыми формами COVID-19 является снижение концентрации провоспалительных цитокинов и нивелирование их действия на организм пациента. Среди лекарственных препаратов, направленных на снижение концентрации провоспалительных цитокинов, нашли применение при COVID-19 ингибиторы ИЛ-6, ИЛ-1, ингибиторы JAK и системные глюкокортикостероиды. Все эти лекарственные препараты в настоящее время назначаются off-label.

Цель – сравнительный анализ по данным литературных источников, представленных в PubMed, клинической эффективности и безопасности использования ингибиторов ИЛ-6, ИЛ-1, JAK и системных глюкокортикостероидов в терапии тяжелых форм COVID-19.

Материалы и методы. Материалами для проведения сравнительного анализа послужили данные литературных источников в системе PubMed, посвященные исследованиям использования системного глюкокортикостероида дексаметазона, ингибитора ИЛ-6 тоцилизумаба, ингибитора ИЛ-1 анакинры и ингибитора JAK – руксолинитиб в терапии тяжелых форм COVID-19. Анализ проводили путем статистической оценки влияния лекарственных препаратов на показатель выживаемости в течение 28 дней среди пациентов с тяжелым течением COVID-19. В качестве статистического инструмента были использованы методики атрибутивной статистики. Оценку безопасности использования лекарственных препаратов проводили путем анализа потенциальных лекарственных взаимодействий. Информацию о потенциальных взаимодействиях лекарственных препаратов получали на специализированном сайте – Drugs.com. Knowmore. Besure (https://www.drugs.com/interaction/list/).

Результаты. В ходе проведенного анализа установлено, что наибольшие показатели эффективности имеет тоцилизумаб, далее следует дексаметазон. Показатель атрибутивной эффективности и значения 95% доверительный интервал для обоих лекарственных препаратов оказался статистически значимым. Показатели относительной и популяционной атрибутивной эффективностей также выше для тоцилизумаба, однако, 95% доверительный интервал этих показателей попадают в область статистически незначимых значений, что требует дополнительных подтверждений их эффективности. Согласно полученным данным, эффективность использования тоцилизумаба выше эффективности других сравниваемых лекарственных препаратов. NNT (дексаметазон) – 32; NNT (тоцилизумаб) – 4, NNT (руксолитиниб) – 7; NNT (анакинра) – 35.

Заключение. Выбор лекарственного препарата должен осуществляться исходя из состояния пациента, сопутствующих заболеваний и используемых в терапии лекарственных препаратов с целью минимизации риска нежелательных межлекарственных взаимодействий. Для ингибитора ИЛ-1 анакинры на фоне самой низкой эффективности среди сравниваемых лекарственных препаратов установлена высокая эффективность для пациентов с сопутствующими гепатобилиарными расстройствами и ДВС-синдромом, что делает ее препаратом выбора среди пациентов с данными состояниями и заболеваниями при развитии «цитокинового шторма».

Ключевые слова: тяжелые формы COVID-19; системный глюкокортикостерод; ингибитор ИЛ-6; ингибитор ИЛ-1; ингибитора JAK; «цитокиновый шторм»; атрибутивная статистика; межлекарственные взаимодействия

INTRODUCTION

COVID-2019 is currently a global social problem that is particularly challenging for health systems [1].

Regarding a part of medicinal preparations (MPs), clinical studies are being conducted to obtain data on the effectiveness of their use in the treatment for COVID-19 [2]. A special feature of COVID-2019 is the possibility of rapid development of severe and critical conditions, which are characterized by high mortality rates, more specifically, from 49% [3] to 60.5% [4].

Severe and critical forms of COVID-19 are beset by the development of “a cytokine storm”, which is characterized by an increased secretion of proinflammatory cytokines. Therefore, one of the leading strategies for

treating patients with severe forms of covid-19 is the reduction of concentration of proinflammatory cytokines and leveling out their effect on the patient. [5].

Among the drugs aimed at reducing the concentration of proinflammatory cytokines, IL-6 inhibitors, IL-1 inhibitors, JAK inhibitors and systemic glucocorticosteroids have been found useful in COVID-19. All of these drugs are currently prescribed off-label. More research on the efficacy and safety of these drugs in COVID-19 therapy, is currently being conducted.

THE AIM of the work is a comparative analysis of the clinical efficacy and safety of IL-6, IL-1, JAK inhibitors and systemic glucocorticosteroids in the treatment for severe forms of COVID-19, according to the literature presented in PubMed.

MATERIALS AND METHODS

The materials for the comparative analysis were the data from the literature sources published in the PubMed system and devoted to 4 studies of the use of the systemic glucocorticosteroid dexamethasone [6], the IL-6 inhibitor tocilizumab [7], the IL-1 inhibitor anakinra [8] and the JAK inhibitor ruxolitinib [9] in the treatment of severe forms of COVID-19, including the analysis of the therapy data of 7406 patients. The selected sources contain comparable study endpoints (a drug effect on the 28-day survival).

The analysis was carried out by statistical evaluation of the drugs effect within the 28-day survival rate among the patients with severe COVID-19. The methods of attribute-based statistics were used as a statistical tool. The basis of the analysis with the use of attribute-based statistics is a contingency table (Table 1).

After compiling a contingency table, the following hypothesis has been formed: the use of the studied MPs makes it possible, to a greater extent, to achieve an increase in the survival rate within 28 days among the patients with a severe COVID-19 course compared to the controls.

The first stage is to determine the absolute efficacy (AE), which comes to calculating the frequency of the onset of positive clinical effects in the groups of patients who received and who did not receive MPs. Formula 1 was used to find the frequency of positive clinical outcomes in the exposed group (the patients receiving MPs) for each of the analyzed drugs.

$$AEe = \frac{a}{A} \quad (1)$$

Similarly, according to Formula 2, the frequency of occurrence of positive clinical effects in the unexposed group (the patients who did not receive MPs), was calculated.

$$PEn = \frac{c}{B} \quad (2)$$

As a result, the point estimates of the onset of positive clinical outcomes from the prescription of therapy regimens were obtained, including and not including the analyzed MPs (exposed and unexposed groups of patients). These frequencies were calculated on the basis of not the entire population, but only on its representative part, which approximately reflects the properties of the population. These point estimates were subjected to a statistical error. Therefore, the standard error of the obtained AEs was further calculated.

Since the obtained frequencies can change while calculating on another sampling, it was determined how significant these changes would be, and what minimum intervals of values would cover the actual exact values of the sought frequencies. In other words, what is the minimum interval that contains the real value of the sought frequency with a probability of 95% was to be determined. In statistics, this kind of interval is statistically 95% and is called “a confidence interval” (95% CI).

At the next stage, the attribute-based efficacy (AbE) was calculated. It characterizes the part of the efficacy (its share) that is associated with the studied MP and is explained by it. AbE was calculated according to Formula 3.

$$AbE = AEe - PEn = \frac{a}{c} - \frac{c}{B} \quad (3)$$

Based on the calculation of the relative efficacy (RE) according to Formula 4, the bonding force between the effect of MPs on the treatment and the outcome was shown, i. e., how many times the clinical efficacy of the therapy increases when the analyzed MPs are used.

$$RE = \frac{AEe}{PEn} = \frac{a/A}{c/B} \quad (4)$$

Population attribute-based efficacy (PAbE) is the absolute difference in indicators in the whole population and in the unexposed group. PAbE is similar to AbE but unlike the latter. It characterizes the population component of efficacy (Formula 5).

$$PAbE = \frac{C}{Q} = \frac{c}{B} \quad (5)$$

The safety assessment of the MPs products was carried out by analyzing potential drug- interactions. The information about potential drug interactions was obtained on a specialized website – Drugs.com. Know-more. Besure (https://www.drugs.com/

RESULTS

Statistically significant indicators are AbE, RE, and PAbE (Table 2).

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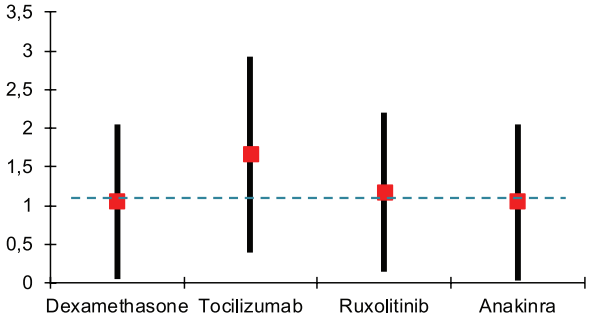

Figure 1 – Corridors of fluctuations in RE values with 95% CI of the MPP effect on the survival rates within 28 days

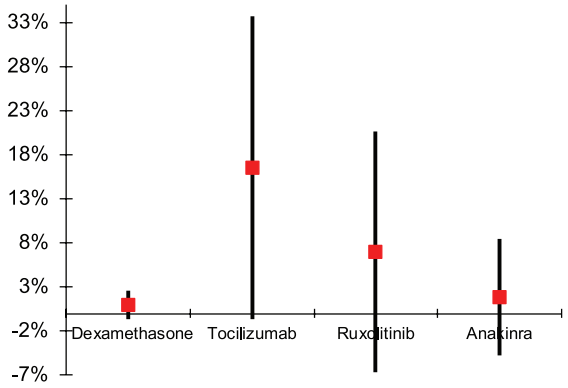

Figure 2 – Corridors of fluctuations in PAbE values with 95% CI of the effect of the studied drugs on the survival rate in the treatment of severe forms of COVID-19

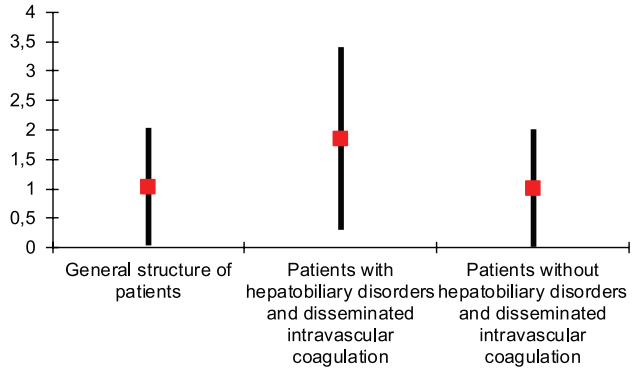

Figure 3 – Corridors of fluctuations in RE values with 95% CI of the effect of anakinra on survival rates within 28 days in different groups of patients

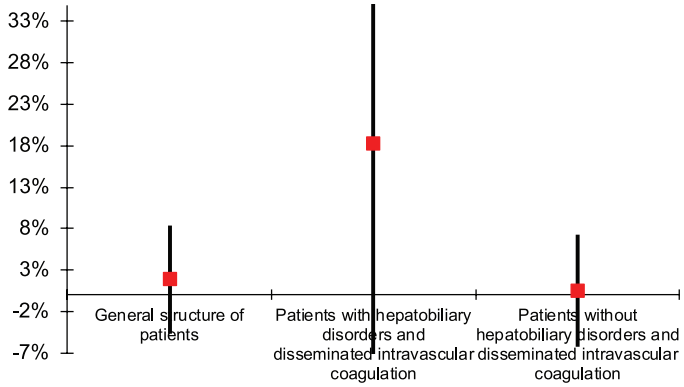

Figure 4 – Corridors of fluctuations in PAbE values with 95% CI of the anakinra effect on the survival rate in the treatment for severe forms of COVID-19 in different groups of patients

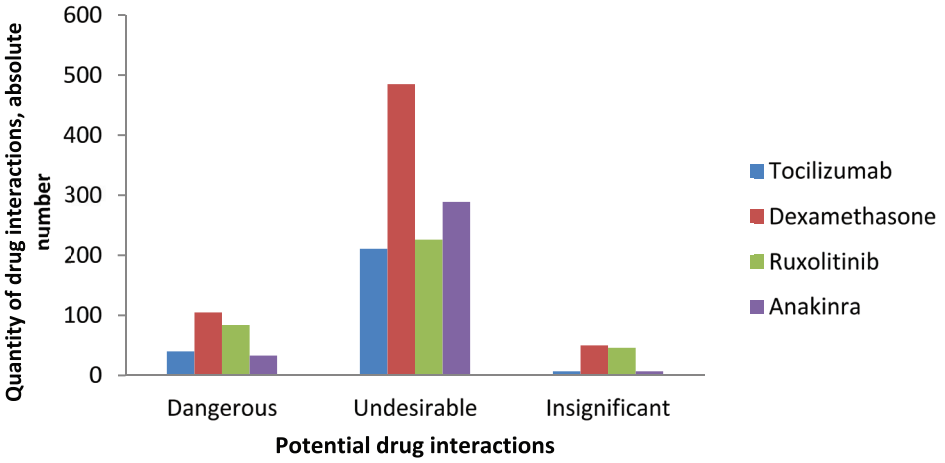

Figure 5 – Potential drug interactions of the drugs aimed at eliminating "the cytokine storm" in the treatment for severe COVID-19 conditions

Note: according to the specialized site – Drugs.com.Knowmore. Besure (URL: https: //www.drugs.com/interaction/list/)

Table 1 – Contingency table

Studied MP	Hypothetical effect of the studied drug		Total
	Yes	No	
Yes	**(a)** Group **in** a hypothetical state **with the effect** of the studied MP	**(b)** Group **out of** hypothetical state **with the effect** of the studied MP	**(A)** Sum a+b
No	**(c)** Group **in** a hypothetical state **without the effect** of the studied MP	**(d)** Group **out of** hypothetical state **without the effect** of the studied MP	**(B)** Sum c+d
Total	**(C)** Sum a+c	**(D)** Sum b+d	**(Q)** Sum A+B or C+D

Table 2 – The results of evaluating the clinical efficacy of various drugs in terms of survival within 28 days in the treatment for severe forms of COVID-19

Statistical value	MPs			
	Dexamethasone	Tocilizumab	Ruxolitinib	Anakinra
Attribute-based efficacy	3.1%	22.5%	14.3%	2.8%
Relative efficacy	1.04	1.66	1.17	1.04
Population attribute efficacy	1%	16.5%	7%	1.9%
NNT	**32**	**4**	**7**	**35**

Table 3 – The results of the clinical efficacy estimation of (anakinra's IL-1 inhibitor) in terms of the survival rate within 28 days in the treatment for severe forms of COVID-19 in patients with hepatobiliary dysfunction and disseminated intravascular coagulation

Statistical value	IL-2 inhibitor (anakinra)		
	General structure of patients	Patients with hepatobiliary disorders and disseminated intravascular coagulation	Patients without hepatobiliary disorders and disseminated intravascular coagulation
Attribute-based efficacy	2.8%	30.1%	0.8%
Relative efficacy	1.04	1.85	1.01
Population attribute efficacy	1.9%	18.2%	0.5%
NNT	**35**	**3**	**125**

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Table 4 – Drug interactions aimed at eliminating "the cytokine storm" in the treatment for severe COVID-19 conditions

Drug interactions		Level (significance) of clinical interaction	Potential risk of clinical interaction
Dexamethasone	**Tocilizumab**	–	–
	Ruxolitinib	Undesirable	CYP450 3A4 inducers can reduce the concentration of ruxolitinib in the blood plasma; ruxolitinib is metabolized by isoenzyme.
	Anakinra	–	–
Tocilizumab	Dexamethasone	–	–
	Ruxolitinib	–	–
	Anakinra	Dangerous (life – threatening, should be avoided)	There is a risk of increased immunosuppression and an increased risk of developing an infectious process. Treatment with IL-6 inhibitors has been associated with serious, potentially life-threatening and fatal infections, including tuberculosis, invasive fungal infections such as candidiasis, aspergillosis and pneumocystosis, and other opportunistic infections. Cases occurred mainly in the patients administdated with concomitant immunosuppressive drugs or corticosteroids.
Ruxolitinib	Dexamethasone	Undesirable	CYP450 3A4 inducers can reduce the concentration of ruxolitinib in the blood plasma; ruxolitinib is metabolized by isoenzyme.
	Tocilizumab	–	–
	Anakinra	Undesirable	The use of interleukin-1 blockers with other immunosuppressive or myelosuppressive agents can increase the risk of infection. Interleukin-1 blockade can cause neutropenia and severe infections by itself, and the risk may be increased with another kind of immunosuppressive therapy.
Anakinra	Dexamethasone	–	–
	Tocilizumab	Dangerous (life – threatening, should be avoided)	There is a risk of increased immunosuppression and an increased risk of developing an infectious process.
	Ruxolitinib	Undesirable	The use of interleukin-1 blockers with other immunosuppressive or myelosuppressive agents can increase the risk of infection. Interleukin-1 blockade can cause neutropenia and severe infections by itself, and the risk may be increased with another immunosuppressive therapy.

Note: according to the specialized site – Drugs.com.Knowmore. Besure (URL:https://www.drugs.com/interaction/list/)

Table 5 – Potential drug interactions to be avoided in the treatment for severe COVID-19 conditions (drugs, the concomitant administration of which should be avoided: dangerous life-threatening clinically significant interaction)

Dexamethasone	Tocilizumab	Ruxolitinib	Anakinra
Fluroquinolone	Anakinra -	Clarithromycin	Tocilizumab
Amiodarone-	–	Fluconazole	–
–	–	Itraconazole	–
–	–	Ketoconazole	–
–	–	Voriconazole	–

For dexamethasone, AbE was 3.1% (95% CI 0.9% – 5.3%); for tocilizumab it was 22.5% (95% CI 4.6% – 40.4%); for ruxolitinibruxolitinib AbE was 14.3% (95% CI –1.7% – 30.2%); for anakinra it was 2.8% (95% CI -4.2% – 9.8%). This indicator is statistically significant for dexamethasone and tocilizumab.

As for the relative efficacy (RE), for dexamethasone it was 1.04 (95% CI 0.040 to 2.042); for tocilizumab – 1.66 (95% CI 0.400 to 2.917); for ruxolitinibruxolitinib – 1.17 (95% CI 0.139 to 2.194); for anakinra, RE was 1.04 (95% CI 0.038 to 2.046) (Fig. 1).

However, the lower limits of 95% of the confidence interval (CI) fall in the area of the negative values <1, which does not make it possible to consider this indicator statistically significant.

For the compared MPs, the lower limit of 95% of PAbE CI also falls into the area of the negative values, which does not make it possible to assert the statistical significance of the obtained indicator and requires additional confirmations (Fig. 2).

Comparing the 95% CI values for RE and PAbE, it is possible to speak of a greater advantage of the IL-6 inhibitor relative to the other analyzed MPs.

The Number Needed to Treat (NNT), the average indicator of the number of the patients who need to be treated with this drug, was also calculated to prevent one additional episode compared to the control group). For dexamethasone, the NNT is 32; for tocilizumab it is 4; for ruxolitinib – 7; for anakinra – 35. According to the data obtained, the effecacy of tocilizumab is higher than that of the other compared MPs. According to the results of the calculations, it is anakinra that has the lowest effecacy. However, the study carried out by Shakoory et al. [8], showed its high efficacy in terms of the survival rate within a 28-day period among the patients with disseminated intravascular coagulation (DIC) and hepatobiliary dysfunction (Table 3).

The results obtained, make it possible to speak about the choice of anakinra in the patients with severe forms of COVID-19, associated with disseminated intravascular coagulation, as well as with liver diseases.

RE of anakinra among the patients with concomitant is more than 1.5 times higher compared with the general structure of patients (Fig. 3).

The PAbE indicator is more than 9 times higher (Fig. 4).

According to the electronic resource Drugs.com, the data of the previous studies were the following: for dexamethasone, 640 potential interactions were identified, 105 of which were clinically dangerous, 485 were undesirable; for tocilizumab, 258 potential interactions were identified, 40 of which were clinically dangerous, 211 were undesirable; for ruxolitinib, 356 potential interactions were identified, 84 of which were clinically dangerous, 226 were undesirable; for anakinra, 329 potential interactions were identified, 33 of which were clinically dangerous, 289 were undesirable (Fig. 5).

In the course of the study, drug interactions aimed at eliminating "the cytokine storm" in the treatment for severe COVID-19 conditions which could potentially occur in a hospital, were also analyzed (Table 4).

Potential drug interactions that should be avoided and that can often occur when treating the patients for severe COVID-19, have also been identified (Table 5).

For example, fluoroquinolone therapy could take place in the treatment for pneumonia in the patients with COVID-19. In this case, against the background of the fluoroquinols use, the prescription of dexamethasone is dangerous.

A certain danger is represented by the use of glucocorticosteroid dexamethasone in the infectious process. It contributes to the development of secondary infections, superinfections. However, the data presented in a systematic review on the use of corticosteroids in the treatment for sepsis, show no statistically significant difference in the incidence of superinfection with long-term low-dose courses of glucocorticosteroids (16.75% versus 16.11%) [10].

DISCUSSION

On 2 September, 2020, WHO published guidelines for the use of corticosteroids in patients with COVID-19. WHO recommends systemic corticosteroids for the treatment of patients with severe and critical (gravy) COVID-19. Herewith, it is not recommended to use corticosteroids in the treatment of patients with mild forms of COVID-19, as this is not beneficial and may aggravate a patient's condition [11].

Corticosteroid therapy should be used with an extreme caution in the patients with diabetes mellitus. The fact that among patients with a severe course of COVID-19 there are people with diabetes mellitus, should be taken into consideration. Then, when planning purchases as well as the budget, it is necessary to take into account the availability of tocilizumab to stabilize the condition of patients with a developed "cytokine storm". In such cases, the use dexamethasone is dangerous.

When tocilizumab was used, superinfection developed twice as often compared with controls in the patients with COVID-19 who were on artificial lung ventilation (ALV) (54% versus 26%) [7]. Herewith, no statistically significant change in mortality within 28 days was found in the group of patients with superinfection and without it.

A particular risk from COVID-19 is the transition of patients to grave and critical conditions. The hospitalized patients with a diagnosis of severe COVID-19, have increased levels of cytokines. This increase may be associated with a cytokine release syndrome ("cytokine storm"), which is triggered by a number of factors (sepsis, cancer, organ transplantation), and in particular, viral infection [12]. The pathogenesis is based on a violation of the mechanisms of cellular cytotoxicity, an excessive

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activation of cytotoxic lymphocytes and macrophages with a massive release of pro-inflammatory cytokines (a tumor necrosis factor (TNF-α), interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), a granulocyte colony-stimulating factor, monocytic chemoattractive protein 1), and inflammatory markers (C-reactive protein, serum ferritin), infiltration of internal organs and tissues activated by T-lymphocytes and macrophages – all these factors lead to a high-intensity inflammatory response [13, 14].

There is evidence of the successful use of an IL-1 receptor antagonist in the development of "a cytokine storm" [15]. The analysis of the data from phase III randomized study of the use of an IL-1 receptor antagonist (anakinra), indicates a significant improvement in the survival and the absence of serious adverse reactions in the patients with the development of sepsis [8]. Therefore, the use of an IL-1 receptor antagonist in severe forms of COVID-19, may be a promising direction in therapy and requires additional research.

A special place in the development of "the cytokine storm" in patients with COVID-19, belongs to IL-6, therefore, the effect on IL-6 and/or the mechanisms associated with its production, are the point of application in the treatment for severe patients. Interleukin 6 (IL-6) blockers are used to treat the "cytokine storm" in COVID-19 [16]. Thus, tocilizumab, which is a recombinant humanized monoclonal antibody that antagonizes the IL-6 receptor and is used, as recommended, in the treatment for rheumatoid arthritis, may play a key role in the treatment for critically ill patients with COVID-19 [17]. When using tocilizumab, an improvement in the main indicators during COVID-19 and a decrease in mortality in severe and critical conditions, has been shown [18].

CONCLUSION

In the course of the analysis, it was found out that the IL-6 inhibitor tocilizumab has the highest efficacy indicators, followed by the systemic glucocorticosteroid dexamethasone. The AbE and 95% CI values for the both drugs were statistically significant. The RE and PAbE values, are also higher for tocilizumab, however, 95% of the CIs of these indicators, fall into the area of statistically insignificant values, which requires additional confirmation of their efficacy. The choice of MPs should be based on a patient's condition, comorbidities and the drugs used in therapy, in order to minimize the risk of undesirable drug interactions.

Against the background of the lowest efficacy among the compared MPs, for the IL-1 inhibitor anakinra, its high efficacy was established for the patients with concomitant hepatobiliary disorders and disseminated intravascular coagulation, which should be taken into account when treating such patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

CONTRIBUTION OF AUTHORS

Zhukova O.V. – collection, processing of material, statistical processing, text writing;
Kagramanyan I.N. – text writing, editing;
Khokhlov A.L. – the concept and design of the study.

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