RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

CLINICAL AND ECONOMIC ANALYSIS OF GENETICALLY ENGINEERED BIOLOGICS CONSUMPTION BY PATIENTS WITH COVID-19

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Received 21 Feb 2022 After peer review 15 March 2022 Accepted 20 Apr 2022

The aim of the article is a comparative clinical and economic assessment of genetically engineered monoclonal antibodies against interleukins in infectious diseases facilities in Volgograd region, reassigned to treat COVID-19 patients.

Materials and methods. ABC analysis of the drug consumption in infectious disease facilities in Volgograd region in 2020 and 2021, cost-minimization analysis, and volume of consumption (standard dose per 1000 patients) for genetically engineered monoclonal antibodies against interleukins, were performed on the basis of pharmacies dispensing drug reports on infectious diseases facilities, Russian State Register of maximum selling prices, and Russian guidelines for COVID-19 treatment.

Results. Only a small proportion of COVID-19 patients (43.6 standard doses per 1000 patients in 2020 and 137.8 per 1000 patients in 2021) received genetically engineered biologics in infectious disease facilities in Volgograd Region. Nevertheless, in the studied facilities, medical drug expenses on them exceeded from 20% in 2020 to 40% of the total inventory value in 2021. In mild COVID-19 patients with a high comorbidity index, netaquimab was the least expensive drug therapy and levilimab was the most expensive one. For moderate COVID-19, a standart recommended dose of sarilumab was the least expensive among the drugs used in the studied facilities, and anakinra was the least expensive drug among all the recommended GEBs. In severe and extremely severe COVID-19 courses, tocilizumab and sarilumab were less the least expensive among the GEBs used in the infectious disease facilities, and anakinra was the least expensive among all the recommended GEBs.

Conclusion. Accepting a possible equal effectiveness based on the currently available data, sarilumab is the least expensive for moderate COVID-19 and tocilizumab is the least expensive for severe and extremely severe COVID-19.

Keywords: genetically engineered biologics; interleukin antagonists; COVID-19; ABC-analysis; cost-minimization analysis

Abbreviations: GEB(s) – genetically engineered biologics; IL(s) – interleukins; IgG – immunoglobulin G; MA(s) – monoclonal antibodies; INN – international nonproprietary name; VED – vital and essential medicines; RF – Russian Federation; SD – standard dose; CI – confidence interval; RR – relative risk.

КЛИНИКО-ЭКОНОМИЧЕСКИЙ АНАЛИЗ ПОТРЕБЛЕНИЯ ГЕННО-ИНЖЕНЕРНЫХ БИОЛОГИЧЕСКИХ ПРЕПАРАТОВ ПАЦИЕНТАМИ С COVID-19

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Получена 21.02.2022 После рецензирования 15.03.2022 Принята к печати 20.04.2022

For citation: V.I. Petrov, A.Yu. Ryazanova, A.V. Ponomareva, O.V. Shatalova, Ya.V. Levina. Clinical and economic analysis of genetically engineered biologics consumption by patients with COVID-19. *Pharmacy & Pharmacology.* 2022;10(2):198-206. **DOI:** 10.19163/2307-9266-2022-10-2-198-206

Для цитирования: В.И. Петров, А.Ю. Рязанова, А.В. Пономарева, О.В. Шаталова, Я.В. Левина. Клинико-экономический анализ потребления генно-инженерных биологических препаратов пациентами с COVID-19. *Фармация и фармакология.* 2022;10(2):198-206. **DOI:** 10.19163/2307-9266-2022-10-2-198-206

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2022-10-2-198-206

Цель. Сравнительный клинико-экономический анализ применения генно-инженерных биологических препаратов антагонистов интерлейкинов в инфекционных отделениях Волгоградской области, перепрофилированных для лечения пациентов с COVID-19.

Материалы и методы. На основании отчётно-учётной документации по выдаче лекарственных средств в отделениях, Государственного реестра, предельных отпускных цен и временных методических рекомендаций по лечению COVID-19, проведён АВС-анализ расходования лекарственных средств в инфекционных отделениях Волгоградской области в 2020 и 2021 гг., выполнен анализ минимизации затрат и рассчитан объём потребления генно-инженерных биологических препаратов, антагонистов интерлейкинов (стандартная доза на 1000 пациентов).

Результаты. В инфекционных отделениях Волгоградской области только небольшая доля пациентов с COVID-19 (43,6 стандартных доз на 1000 больных 2020 г. и 137,8 на 1000 больных в 2021 г.) получала генно-инженерные биологические препараты. Тем не менее, расходы на них в изучаемых отделениях в 2020 году превысили 20%, а в 2021 г. – 40% от всех расходов на лекарственные средства. При лёгком течении COVID-19 у пациентов с высоким индексом коморбидности наименьшей стоимостью на курс терапии обладал нетакимаб, а наибольшей стоимостью – левилимаб. При среднетяжёлом течении COVID-19 среди препаратов, закупаемых отделениями, наименьшей стоимостью 1 введения обладал сарилумаб, а среди всех рекомендованных препаратов – анакинра. При тяжёлом и крайне тяжёлом течении, наименьшей стоимостью 1 введения обладали тоцилизумаб и сарилумаб, а среди всех рекомендованных препаратов – анакинра.

Заключение. При равной эффективности на основании имеющихся в настоящий момент данных при среднетяжёлом течении COVID-19 экономически наиболее оправдано применение сарилумаба, а при тяжёлом и крайне тяжёлом течении – тоцилизумаба.

Ключевые слова: генно-инженерные биологические препараты; антагонисты интерлейкинов; COVID-19; АВС-анализ; анализ минимизации затрат

Список сокращений: ГИБП – генно-инженерные биологические препараты; ИЛ – интерлейкины; IgG – иммуноглобулин G; МА – моноклональные антитела; ЛС – лекарственные средства; МНН – международное непатентованное название; ЖНВЛС – жизненно необходимые и важнейшие лекарственные средства; РФ – Российская Федерация; СД – стандартная доза; ДИ – доверительный интервал; ОР – относительный риск.

INTRODUCTION

In the winter and spring of 2020, a wave of a rapidly progressing respiratory failure and deaths from a COVID-19 infection spread in many countries. In February 2022, the COVID-19 mortality in the Russian Federation was 2.4%. In the Volgograd region, it achieved 3.7%[1]. The resources of most countries in the world are now oriented to the novel infection`s treatment. Medical costs for COVID-19 therapy, as well as its effectiveness, are also of interest to the healthcare system.

In the first versions of Russian guidelines on the management of COVID-19 patients[2], the main emphasis was made on antiviral and symptomatic therapy. The discovery of the role of the hyperimmune response or cytokine storm as the basis for the pathogenesis of acute respiratory distress syndrome and multiorgan dysfunction in COVID-19 prompted the initiation of tocilizumab as preventive anti-inflammatory therapy. Anti-inflammatory drugs widely used in rheumatology, such as corticosteroids, Janus kinase inhibitors, tocilizumab and other genetically engineered biologics (GEBs), became the basis of pathogenetic therapy of the novel infection in hospitals in many countries in the world and the Russian Federation, as well. In the 14th version of Russian guidelines on the management of COVID-19 patients[3], janus kinase inhibitors and GEBs in combination with corticosteroids are indicated in patients hospitalized both with mild COVID-19 with risk factors of a severe disease, and with a moderate or severe disease. In the latter cases, the prescription of GEBs is preferred.

In the rheumatology practice, the first GEB infliximab, a monoclonal antibody to the tumor necrosis factor-alpha, was approved for a clinical use in 1998. In the 2000s, when infliximab was not effective, monoclonal antibodies (MAs) that block the action of interleukins (IL), such as IL-6, IL-1 and IL-17, began to be used [1, 2].

IL-6 is a multifunctional cytokine produced by various cell types, and it is involved in the paracrine regulation, systemic physiological and pathological processes such as stimulation of immunoglobulin secretion, activation of T cells, and stimulation of the acute phase inflammatory proteins production in the liver and stimulation of hematopoiesis. IL-6 is involved in the pathogenesis of various diseases, playing an important role in the development of the “cytokine storm” in the novel coronavirus infection COVID-19. IL-1β induces gene expression and production of inflammatory mediators such as IL-6 and cyclooxygenase-2. IL-17A, a proinflammatory cytokine, stimulates T-cell immunity and increased the production of inflammatory mediators: IL-1, IL-6, the tumor necrosis factor alpha, and other [3, 4].

The first reports on the successful usage of tocilizumab (MA to IL-6 receptor) in patients with severe COVID-19, were published by Chinese researchers just after the start of the COVID-19 pandemic caused by the SARS-CoV-2 virus [5, 6]. Subsequently, the efficiency of the drug was demonstrated in numerous observational studies conducted in different countries including the Russian Federation [7–9].

[1] Operational data: Coronavirus COVID-19. Official information about coronavirus in Russia at stopcoronavirus.rf. Available from: https://xn--80aesfpebagmfblc0a.xn--p1ai/information/.

[2] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 4 (27 March 2020). Ministry of Health of the Russian Federation; 2020.

[3] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 14 (27.12.2021). Ministry of Health of the Russian Federation; 2021.

Currently, in addition to tocilizumab in the 14th version of Russian guidelines on the management patients with COVID-19[4], there were also 6 other anti-inflammatory GEBs including three Russian biosimilars (Table 1), two of which were registered at the outbreak of the COVID-19 pandemic. On February 22, 2022, a new version of Russian guidelines was issued, there the treatment regimens for COVID-19 patients did not include netakimab[5].

THE AIM of the study was to perform a comparative clinical and economic assessment of genetically engineered monoclonal antibodies against interleukins in infectious diseases facilities in Volgograd region, reassigned to treat patients with COVID-19 in 2020–2021.

MATERIALS AND METHODS

For ABC analysis of the drug consumption in infectious disease facilities in Volgograd region, pharmacies dispensing drug reports in 2020 and 2021, were used. According to international nonproprietary names (INNs), all items were ranged in compliance with the expired costs from the highest to the lowest; the costs were calculated for each INN as a percentage of the total inventory value and the cumulative percentage.

Groups of the drugs that account for 80% of the total inventory (segment A), 15% of the total inventory (segment B), and 5% of the total inventory (segment C), were identified and the percentage of consumption within each group was determined.

The recommended doses of GEBs for different COVID-19 severity were calculated according to the 14th version of Russian guidelines on the management patients with COVID-19[6]. The costs of 1 GEB injection or 1 therapy course were calculated according to the pharmacies dispensing drug reports on infectious disease facilities in 2020 and 2021, as well as on the basis of the Russian Register of maximum selling prices[7]. Due to the fact that in the treatment of COVID-19, the studied drugs in most cases are prescribed as a single injection (not daily), and according to the low frequency of these drugs usage in real clinical practice, in order to estimate the volume of consumption, the indicator Standard Dose per 1000 treated patients was calculated. The Standard Dose of 1 administration or course of therapy SD was determined according to the recommended single or course dose for mild and moderate COVID-19. For tocilizumab, 1 SD was 320 mg (16 ml of 20 mg/ml concentrate), olokizumab – 64 mg (1 vial, 160 mg/ml – 0.4 ml), levilimab – 324 mg (2 syringes of 180 mg/ml – 0.9 ml each), sarilumab – 400 mg (2 syringes of 175 mg/ml – 1.14 ml each) and secukinumab – 300 mg (2 syringes of 150 mg/ml – 1 ml each). In terms of US dollars (USD), the exchange rate of 1 ruble = 0.012 USD on February 25, 2022 was used.

RESULTS

In 2020, about 30 million rubles (USD 360 000) were spent on 117 INN drugs in 5 infectious disease facilities, including over 8 million rubles (USD 96 000) of anti-inflammatory therapy (corticosteroids, janus kinase inhibitors and GEBs) (27.0% of the total inventory value). About 7 million rubles (USD 84 000) out of this sum was spent on GEBs (23.4% of the total inventory value). In 2021, about 80 mln rubles (USD 960 000) was spent in 4 infectious disease facilities on 129 INN drugs. Out of this sum, a little over 36 mln rubles (USD 432 000) (45.9% of the total inventory value) was spent for anti-inflammatory therapy with 5 GEBs (32.6 mln rubles; USD 391 200 – 41.5% of the total inventory value).

In 2020, 51.8% of the Segment A value was represented by antibacterials (RUB 12 494 680/ USD 149 936); 26.5% – by antimicrobials (RUB 6 395 410/ USD 76 745); 14.5% – by anticoagulants (RUB 3 494 986/ USD 41 940). In 2021, 49.2% of the Segment A value was represented by antiplatelet agents (RUR 31 325 961/ USD 375 912); 37.2% – by anticoagulants (RUR 23 641 908/ USD 283 703); 13.6% – by antibiotics (RUR 8 653 352/ USD 103 840) (Table 2).

In 2020, according to Russian guidelines, 3 GIBPs out of 5 (possible at the end of 2020) were purchased in the facilities. 77 vials of olokizumab (64 mg, 160 mg/ml – 0.4 ml), 64 concentrates of tocilizumab (400 mg, 20 mg/ml – 20 ml) and 10 packages of levilimab (2 syringes 162 mg, 180 mg/ml – 0.9 ml) were used. In 2021, 4 out of 7 GEBs presented in Russian guidelines, were procured. 413 vials of olokizumab (64 mg, 160 mg/ml – 0.4 ml), 14 concentrates of tocilizumab (400 mg, 20 mg/ml – 20 ml) and 20 (80 mg, 20 mg/ml – 4 ml), 197 packages of levilimab (2 syringes 162 mg, 180 mg/ml – 0.9 ml), 35 packages of sarilumab (2 syringes 200 mg, 175 mg/ml – 1.14 ml), and 10 syringes of secukinumab (150 mg/ml – 1 ml) were used (Fig. 1).

According to Russian guidelines[8], the choice of GEBs and dosing regimen depend on the severity of COVID-19. A cost minimization analysis in mild COVID-19 patients with a high comorbidity index revealed that baricitinib, a Janus kinase inhibitor, an alternative to GEB in this particular group of patients, had the lowest cost per

[4] Ibid.

[5] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 15 (22.02.2022). Ministry of Health of the Russian Federation.; 2022.

[6] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 14 (27.12.2021). Ministry of Health of the Russian Federation; 2021.

[7] State Register of Medicines. Available from: https://grls.rosminzdrav.ru/Default.aspx.

[8] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 14 (27.12.2021). Ministry of Health of the Russian Federation; 2021.

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DOI: 10.19163/2307-9266-2022-10-2-198-206

course of therapy. Among GEBs in mild COVID-19, the lowest cost per administration was that of netakimab, which was not used in the studied infectious disease facilities. Russian drug levilimab had the highest cost in mild COVID-19. Administration of one standard dose of levilimab in the infectious disease facilities in Volgograd region at the procurement prices, cost more than 57 thousand rubles (684 USD), and in case of ineffectiveness, a patient could need a repeated administration of the drug, which doubled the GEBs cost in this category of patients (Table 3).

For moderate COVID-19, among the drugs procured by the infectious disease facilities, sarilumab had the lowest cost per administration; and among all the recommended GEBs, anakinra had the lowest cost per administration. For severe and extremely severe COVID-19, tocilizumab (the most studied drug for treating COVID-19) and sarilumab had the lowest possible cost per administration among the drugs procured by the infectious disease facilities. Among all the recommended GEBs, anakinra had also the lowest possible cost. According to the maximum prices in the State Register of Medicines (the Register of Vital and Essential Medicines of 2022), the cost of 1 canakinumab injection for severe and extremely severe COVID-19 exceeds 1 million rubles (12 000 USD). The fact makes it impossible to include this medicine in the infectious disease facilities procurement plan because of its extremely high cost.

Table 1 – Anti-inflammatory GEBs recommended for the treatment of COVID-19

INN	Worlds first registration[9] / registration in Russia	Type of monoclonal antibodies	Target	Russian guidelines. Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19)										
				Version 5 08.04.20	Version 6 28.04.20	Version 7 03.06.20	Version 8 03.09.20	Version 9 26.10.20	Version 10 08.02.21	Version 11 07.05.21	Version 12 21.09.21	Version 13 13.10.21	Version 14 27.12.21	Version 15 22.02.22
Tocilizumab	2003/2009	Humanized IgG1	IL-6 soluble and membrane receptors	+	+	+	+	+	+	+	+	+	+	+
Sarylumab	2017/2018	Human IgG1	IL-6 soluble and membrane receptors		+	+	+	+	+	+	+	+	+	+
Olokizumab	No/2020	Humanized IgG4/kappa	Circulating IL-6			+	+	+	+	+	+	+	+	+
Kanakinumab	2009/2012	Human IgG1/kappa	IL-1β (induces IL-6 production)			+	+	+	+	+	+	+	+	+
Levilimab	No/2020	Human IgG1	IL-6 soluble and membrane receptors					+	+	+	+	+	+	+
Netakimab	No/2019	Humanized	IL-17A						+	+	+	+	+	
Anakinra	2001/2021	Recombinant version of the antagonist protein	IL-1α and IL-1β receptors								+	+	+	+
Secukinumab	2015/2016	Human IgG1	IL-17A	Absent Russian guidelines										

[9] DrugBank database. Available from: https://go.drugbank.com/.

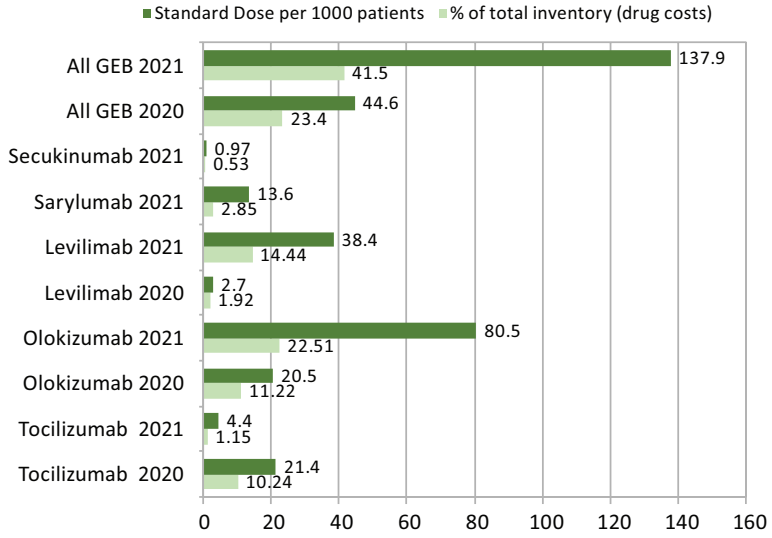

Figure 1 – GEBs consumption in infectious disease facilities in Volgograd region, reassigned to treat COVID-19 patients (2020–2021)

Table 2 – Drug consumption structure in infectious diseases facilities in Volgograd region in 2020-2021

2020 5 infectious diseases facilities 3 750 patients (45 315 days)				2021 4 infectious diseases facilities 5 130 patients (58 439 days)			
INN	Rubles	USD	% per category	INN	Rubles	USD	% per category
Category A 24 089 776 rubles/289 077 USD				**Category A** 63 621 220.88 rubles/763 455 USD			
Meropenem	4 059 700	48 716	16.85%	**Olokizumab**	17 717 700	212612	27.85%
Olokizumab	3 343 260	40 119	13.88%	**Levilimab**	11 364 764	136377	17.86%
Tocilizumab	3 052 150	36 626	12.67%	Sodium Heparin	9 955 524	119 466	15.65%
Cefoperazone Sulbactam	3 049 501	36 594	12.66%	Calcium Nadroparin	6 949 819	83 398	10.92%
Levofloxacin	2 540 382	30 485	10.55%	Enoxaparin	6 736 565	80 839	10.59%
Heparin Sodium	2 538 824	30 466	10.54%	Meropenem	3 600 000	43 200	5.66%
Linezolid	1 592 352	19 108	6.61%	Levofloxacin	3 433 352	41 200	5.40%
Ceftriaxone	1 252 745	15 033	5.20%	**Sarilumab**	2 243 497	26 922	3.53%
Sodium Chloride	1 010 270	12 123	4.19%				
Enoxaparin	956 162	11 474	3.97%	Cefoperazone Sulbactam	1 620 000	19 440	2.55%
Dexamethasone	694 431	8 333	2.88%				
Category B 4 327 479.67 rubles/USD 51 930				**Category B** 11 199 427.98 rubles/USD 134 393			
Interferon Beta-1b	618 984	7 428	14.30%	Dexamethasone	1 542 966	18 516	13.78%
Favipiravir	581 350	6 976	13.43%	Sodium Chloride	1 318 901	15 827	11.78%
Levilimab	571 664	6 860	13.21%	Baricitinib	1 122 851	13 474	10.03%
Azithromycin	527 163	6 326	12.18%	Ceftriaxone	1 121 652	13 460	10.02%
Lopinavir Ritonavir	345 789	4 149	7.99%	**Tocilizumab**	901 725	10 821	8.05%
Propofol	292 905	3 515	6.77%	Remdesivir	895 400	10 745	8.00%
Baricitinib	243 296	2 920	5.62%	Surfactant	696 160	8 354	6.22%
Amoxicillin Clavulanate	177 126	2 126	4.09%	Favipiravir	672 546	8 071	6.01%
Omeprazole	163 793	1 966	3.78%	Omeprazole	669 779	8 037	5.98%
Clopidogrel	163 269	1 959	3.77%	Azithromycin	500 324	6 004	4.47%
Umifenovir	139 440	1 673	3.22%	Propofol	492 577	5 911	4.40%
Methylprednisolone	133 102	1 597	3.08%	Prednisolone	434 442	5 213	3.88%
Vancomycin	129 092	1 549	2.98%	**Secukinumab**	419 400	5 033	3.74%
Insulin	128 818	1 546	2.98%	Methylprednisolone	410 706	4 928	3.67%
Ambroxol	111 689	1 340	2.58%				
Category C 1 383 459.64 rubles/USD16 602 91 INNs				**Category C** 3 893 959.03 rubles/USD 46 728 106 INNs			

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DOI: 10.19163/2307-9266-2022-10-2-198-206

Table 3 – GEBs cost minimization analysis according to COVID-19 severity

INN	Drug formulation and Strengths	Recommended dosage	Repeated dose in case of insufficient effect	Costs per administration or per course (7 or 14 days)			
				Procurement in infectious diseases facilities		List of Vital and Essential Drugs[10] 2022	
				Rubles	USD	Rubles	USD
Mild COVID-19 (patients with high comorbidity index)							
Netakimab*	Syringe 60 mg/1 ml	2 syringes				18 181.82	218
Levilimab	Syringe 162 mg (180 mg/ml – 0.9 ml)	2 syringes	Every 24 hours	57 166.38 (2020) 57 689.16 (2021)	686 692	47 531.10	570
Olokizumab	Vial 64 mg (160 mg/ml, 0.4 ml)	1 vial	Every 24 hours	43 418.96 (2020) 42 900 (2021)	521 515	39 000.00	468
Baricitinib	Tablets 4 mg (packages of 14, 28, 56 tablets)	4 mg/day for 7–14 days		12 164.8–24 329.6 (2020) 12 204.9 – 24 409.8 (2021)	146–292 146–293	10 064.6 – 20 129.20	121–242
Tofacitinib	Tablets 5 and 10 mg (package of 56 tablets)	10 mg twice a day for 7–14 days				20 129.46 – 40 258.92	242–483
Moderate COVID-19							
Levilimab	Syringe 162 mg (180 mg/ml – 0.9 ml)	2 syringes	Every 24 hours	57 166.38 (2020) 57 689.16 (2021)	686 692	47 531.10	570
Olokizumab	Vial 64 mg (160 mg/ml, 0.4 ml)	1–2 vials	Every 12 hours	43 418.96–86 937.92 (2020) 42 900–85 800 (2021)	521–1,043 515–1,030	39 000.00–78 000.00	468–936
Tocilizumab	Syringe 162 mg/0.9 ml (4 pc.)	4 mg/kg 320 mg for 80 kg 2 syringes or 16 ml				26 526.75	318
	Concentrate 20 mg/ml, 2 ml			38 151.88 (2020) 39 298.56 (2021)	458	28 139.984	338
	Concentrate 20 mg/ml, 4 ml			42 800 (2021)	472–514	29 291.08	351
	Concentrate 20 mg/ml, 10 ml					29 291.088	351
Sarylumab	Syringe 200 mg (175 mg/ml, 1.14 ml)	1 syringe	Every 12 hours	32 049.96 (2021)	385	26 493.16	318
Anakinra	Syringe 100 mg (150 mg/ml, 0.67 ml)	100 mg/day subcutaneously for 7 days				14 867.42	178
Severe and extremely severe COVID-19 (pneumonia with respiratory failure, ARDS)							
Tocilizumab	Syringe 162 mg/0.9 ml (4 pc.)	4–8 mg/kg 320–640 mg at a weight of 80 kg 2–4 syringes or 16–32 ml	Every 12 hours			26 526.75–53 053.5	318–637
	Concentrate 20 mg/ml, 2 ml			38 151.88–76 303.75 (2020) 39 298.56–78 597.12 (2021)	458–916 472–943	28 139.984–56 279 968	338–675
	Concentrate 20 mg/ml, 4 ml			42 800–85 600 (2021)	514–1,027	29 291.08–58 582 16	351–703
	Concentrate 20 mg/ml, 10 ml					29 291.088–58 582 176	351–703
Sarylumab	Syringe 200 mg (175 mg/ml, 1.14 ml)	2 syringes	Every 12 hours	64 099.92 (2021)	769	52 986.32	636
Kanakinumab	Vial 150 mg/ml, 1 ml	4–8 mg/kg 2–4 vials at a weight of about 80 kg				1 061 845.34 – 2 123 690.68	12 742–25 484
Anakinra	Syringe 100 mg (150 mg/ml, 0.67 ml)	200 to 400 mg/day subcutaneously For 7 days				29 734.84–59 469.68	357–714
Levilimab	Syringe 162 mg (180 mg/ml – 0.9 ml)	4 syringes	Every 12 hours	114 332.76 (2020) 115 378.32 (2021)	1,372 1,385	95 062.2	1 141
Olokizumab	Vial 64 mg (160 mg/ml, 0.4 ml)	4 syringes		173 875.84 (2020) 171 600 (2021)	2,087 2,059	156 000	1 872
Beyond Guidelines							
Secukinumab	Syringe 150 mg (150 mg/ml, 1 ml)	2 syringes**		83 880 (2021)	1,007	69 097.32	829

Note: * – not present in version 15 of Russian guidelines; ** – the dose used in severe COVID-19 in the study by Hasan M.J. et al. [10].

[10] State register of maximum selling prices. Available from: https://grls.rosminzdrav.ru/PriceLims.aspx.

DISCUSSION

GEBs are now quite widely used to treat various diseases associated with immune inflammation, both in rheumatology, and in gastroenterology, dermatology, pulmonology. GEB therapy of rheumatological patients, patients with severe forms of psoriasis, Crohn's disease, nonspecific ulcerative colitis, bronchial asthma favorably affects the disease prognosis, leads to improved quality of life and achievement of persistent remission [11–16]. More often, GEBs are used as second-line drugs in case of ineffectiveness or poor tolerability of standard baseline anti-inflammatory drugs. The main obstacle to the prescription of GEBs is their high cost, which leads to increased treatment costs and an economic burden on the healthcare system. Nevertheless, in the Russian Federation, a model of clinical and statistical groups has been developed at the federal level, which allows providing the patients requiring GEBs prescription, at the expense of the OMI system [17].

The use of anti-inflammatory GEBs in COVID-19 patients under current conditions of the novel coronavirus infection and the limited evidence base for the treatment of COVID-19 is «off-label» and is based on the international guidelines[9] and consensual expert opinions based on the assessment of the benefit and risk degree in the "off-label" use[10]. In the actual clinical practice, only a small proportion of COVID-19 patients fewer than 4.2% in 2020 and fewer than 13.8% in 2021) in the studied infectious disease facilities received GEBs. Nevertheless, the consumption of these drugs in 2020 exceeded 20%, and in 2021 – 40% of the-total inventory value of the drugs in the OMI system in the studied facilities.

In most cases, the reason for the use of GEBs in COVID-19 patients was fever that did not resolve with the use of systemic corticosteroids (if the drug was available in the facilities), appropriate changes in the inflammatory markers and the absence of contraindications. For two years of the pandemic, more and more publications have become available to evaluate the role of different drugs, including GEBs.

At the beginning of the pandemic, observational studies revealed an association between elevated levels of IL-6 in the severe COVID-19 and the patient mortality [18–20]. A number of the subsequent uncontrolled clinical trials have found a reduction in the disease severity and inflammatory markers after the administration of tocilizumab (MA to IL-6 receptor) [6, 21, 22]. Two major studies, RECOVERY and REMAP-CAP, have demonstrated a significant reduction in mortality after the administration of MA to IL-6 receptor [8, 23].

The RECOVERY study [8] included hospitalized COVID-19 patients who required oxygen support and had C-reactive protein levels ≥ 75 mg/l. The 28-day mortality rate was 31% (621/2022) in the tocilizumab group and 35% (729/2 094) in the standard therapy group (OR 0.85; 95% CI 0.76–0.94; p=0.028). However, this trend was observed only in patients receiving tocilizumab in combination with dexamethasone. The REMAP-CAP study [23] enrolled 2 274 COVID-19 patients requiring a respiratory support (high-flow oxygen therapy, noninvasive or invasive pulmonary ventilation) at the time of inclusion in the study. 972 of these received 1–2 doses of tocilizumab (MA to IL-6 receptor), 485 received sarilumab (MA to IL-6 receptor), 378 received anakinra (MA to IL-1 receptor), and other 418 were included in the control group. In-hospital, survival rates were 66.4% for tocilizumab; 67.3% for sarilumab; 60.3% for anakinra; and 63.1% for controls. Compared with the controls, the mean adjusted odds ratios for the in-hospital survival were 1.42 (95% CI 1.05–1.93) for tocilizumab, 1.51 (95% CI 1.06, 2.20) for sarilumab, and 0.97 (95% CI 0.66, 1.40) for anakinra. Thus, tocilizumab and sarilumab showed a comparable effect in reducing COVID-19 patients' mortality requiring a respiratory support, whereas anakinra showed no positive effect on the severity of COVID-19.

A single-center observational retrospective comparative study of two Russian drugs and tocilizumab in patients with severe COVID-19 was conducted in the Russian Federation [24]. The study included 200 patients with a single administration of tocilizumab (MA to IL-6 receptor), 100 patients who received levilimab (MA to IL-6 receptor) and 100 patients who received olokizumab (MA to IL-6). A comparative analysis of clinical outcomes between the groups revealed a statistically insignificant increase in the risk of sepsis and death in the levilimab group compared to the tocilizumab and olokizumab groups.

The study by Hasan M.J. et al. [10] compared the effectiveness of 300 mg secukinumab (MA to IL 17A) added to baricitinib in the severe course of COVID-19 in 17 patients, compared to the control group that received only baricitinib. The secukinumab+baricitinib group showed a statistically significant reduction in the need for invasive pulmonary ventilation, a shorter ICU stay, and a lower 30-day mortality rate with a greater risk of secondary infections compared to the baricitinib group.

Pavlov R.E. et al. [25] described the experience of using netakimab with corticosteroids in outpatient settings. Netakimab (MA to IL 17A), a Russian drug, a biosimilar of secukinumab, is used for treatment of severe psoriasis forms. The authors conducted a retrospective analysis of treatment of 12 patients with severe COVID-19 who received therapy with netakimab (the first injection of 60–120 mg subcutaneously and, if indicated, the second injection of 60 mg) plus betamethasone dipropionate/betamezon phosphate at the dose of 2 ml (an officinal solution) intramuscularly. The treatment started on the 7th day from the onset of the disease. A repeated administration of netakimab was performed in older patients

[11] COVID-19: clinical guidelines. Available from: https://www.ersnet.org/covid-19/covid-19-guidelines-and-recommendations-directory/.

[12] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 14 (27.12.2021). Ministry of Health of the Russian Federation; 2021.

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DOI: 10.19163/2307-9266-2022-10-2-198-206

due to the insufficient effect in controlling hyperthermia and/or hypoxemia. A simultaneous administration of netakimab and corticosteroids resulted in reducing hyperthermia and/or increased oxygen saturation 2.5 days after the first injection, decreased levels of inflammatory markers, positive dynamics according to the lung computed tomography data. An increased respiratory support (transfer to the artificial lung ventilation) or a change of antibiotic therapy, as well as hospitalization were not required in any case.

Thus, based on the available data, we can conclude that tocilizumab, sarilumab, and probably olokizumab have a comparable efficacy in COVID-19 patients requiring a respiratory support. The extremely high cost of canakinumab raises the question whether it is reasonable to study the effectiveness of this drug in COVID-19 patients. The data obtained on the use of anakinra suggest a lack of efficacy. The efficacy of netakinumab and secukinumab, as well as levilimab, requires a further study.

CONCLUSION

Under conditions of possible equal effectiveness based on the currently available data, the use of sarilumab is the least expensive in moderate COVID-19, and tocilizumab – in severe and extremely severe COVID-19. Among Russian GEBs, the use of olokizumab, compared to levilimab, is the least expensive with possibly higher efficacy and safety. However, the efficacy and safety of anti-inflammatory GEBs in patients with COVID-19, mild COVID-19, requires a further study.

FUNDING

This study had no financial support from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS CONTRIBUTION

Vladimir I. Petrov – development of research design, article editing and its final approval;
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