



COST-MINIMIZATION ANALYSIS OF USING SHORT AND LONG-ACTING ERYTHROPOESIS-STIMULATING AGENTS FOR CORRECTION OF NEPHROGENIC ANEMIA AGAINST THE BACKGROUND OF SUBSTITUTION THERAPY

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Clinical trials conducted in various countries indicate that the use of epoetin alfa in patients with nephrogenic anemia in chronic kidney disease can increase the effectiveness of treatment, reduce the incidence of cardiovascular and infectious complications, and reduce mortality in patients with chronic kidney disease.

The aim of the article was to conduct a comparative clinical and economic assessment of the treatment costs of nephrogenic anemia in adult dialysis patients with recombinant human erythropoietins: epoetin alfa, darbepoetin and long-acting methoxy polyethylene glycol – epoetin beta.

Materials and methods. The study took into account direct medical costs of nephrogenic anemia pharmacotherapy on the basis of 1 year maintenance therapy according to the following scheme: epoetin alfa – 3 times per week, darbepoetin alfa – once per week, methoxy polyethylene glycol – epoetin beta – once per 2 or 4 weeks. A "costs minimization" analysis was performed for equivalent maintenance epoetins doses for intravenous and subcutaneous administrations. Epoetin alfa equivalents were calculated for an average patient weighing 75 kg by converting a weekly dose of short-acting epoetin (7500 IU) into equivalent doses using dose conversion factors.

Results. In the hypothetical cohort of patients under study, epoetin alfa, darbepoetin alfa, and methoxy polyethylene glycol – epoetin beta not differ in effectiveness in achieving target Hb values and in safety. With the equal effectiveness of the investigated drugs, in the studied patients, intravenous epoetin alfa can be less expensive drug therapy relative to the equivalent doses obtained by the calculation: darbepoetin by 14–24% and methoxy polyethylene glycol – epoetin beta by 4–30%. The change-over of patients to the subcutaneous administration makes it possible to decline a weekly dose of epoetin alfa by 20–30% by reducing the frequency of taking the drug to twice a week, and to reduce the cost of drug therapy by a third.

Conclusion. Intravenous and subcutaneous administrations of epoetin alfa 2500 IU may be a more economical drug therapy in comparison with the equivalent doses of darbepoetin and methoxy polyethylene glycol – epoetin beta.

Keywords: chronic kidney disease; anemia; erythropoiesis stimulating agent(s); epoetin alfa; economic assessment

Abbreviations: i.v. – intravenous; DA – darbepoetin; VEDs – vital and essential drugs; RRT – renal replacement therapy; CTs – clinical trials; MP – medicinal preparation; DF – dosage form; INN – international non-proprietary name; VAT – value added tax; s/c – subcutaneous; RCT – randomized controlled trial; r-HuEPO – recombinant human erythropoietin; ESA – erythropoiesis stimulating agent; CKD – chronic kidney disease; CKF – chronic kidney failure; EPO – epoetin.

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АНАЛИЗ МИНИМИЗАЦИИ ЗАТРАТ ПРИМЕНЕНИЯ СТИМУЛЯТОРОВ ЭРИТРОПОЭЗА КОРОТКОГО И ДЛИТЕЛЬНОГО ДЕЙСТВИЯ ДЛЯ КОРРЕКЦИИ НЕФРОГЕННОЙ АНЕМИИ НА ФОНЕ ЗАМЕСТИТЕЛЬНОЙ ТЕРАПИИ

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Клинические исследования, проведенные в различных странах, свидетельствуют о том, что применение эпоэтина альфа у пациентов с нефрогенной анемией при хронической болезни почек может повысить эффективность лечения, снизить число случаев сердечно-сосудистых и инфекционных осложнений, а также смертность у пациентов с хронической болезнью почек.

Цель. Провести сравнительную клинко-экономическую оценку затрат на терапию нефрогенной анемии у взрослых пациентов, находящихся на диализе, рекомбинантными человеческими эритропоэтинами: эпоэтином альфа, дарбэпоэтином и эпоэтином бета (метоксиполиэтиленгликоль) длительного действия.

Методы. В исследовании были учтены прямые медицинские затраты на фармакотерапию нефрогенной анемии из расчета 1 года поддерживающей терапии по схеме: эпоэтин альфа – 3 раза в неделю, дарбэпоэтин альфа – 1 раз в неделю, эпоэтин бета (метоксиполиэтиленгликоль) – 1 раз в 2 недели или 4 недели. Проведен анализ «минимизация затрат» для эквивалентных поддерживающих доз эпоэтинов для внутривенного и подкожного применения. Эквивалентные эпоэтин альфа дозы были рассчитаны для среднестатистического пациента с массой тела 75 кг, путем пересчета недельной дозы эпоэтинов короткого действия (7500 МЕ) в эквивалентные через коэффициенты конвертации доз.

Результаты. У исследуемой гипотетической когорты больных эпоэтин альфа, дарбэпоэтин альфа и эпоэтин бета (метоксиполиэтиленгликоль) не отличаются по эффективности в достижении целевых значений Hb и безопасности. При равной эффективности исследуемых препаратов, эпоэтин альфа внутривенно может являться у исследуемых больных менее затратной лекарственной терапией относительно эквивалентных доз, полученных расчетным путем: дарбэпоэтин альфа на 14–24% и эпоэтина бета (метоксиполиэтиленгликоль) – на 4–30%. Перевод больных на подкожное введение позволяет снизить недельную дозу эпоэтина альфа на 20–30% за счет снижения частоты приема препарата до 2 раз в неделю, и сократить стоимость лекарственной терапии на треть.

Заключение. Эпоэтин альфа 2500 МЕ при внутривенном и подкожном введении может являться более экономичной лекарственной терапией в сравнении с эквивалентными дозами дарбэпоэтина и эпоэтина бета (метоксиполиэтиленгликоль).

Ключевые слова: хроническая болезнь почек; анемия; средства, стимулирующие эритропоэз; эпоэтин альфа; экономическая оценка

Список сокращений: в/в – внутривенный; ДА – дарбэпоэтин; ЖНВЛП – жизненно необходимые и важнейшие лекарственные препараты; ЗПТ – заместительная почечная терапия; КИ – клинические исследования; ЛП – лекарственный препарат; ЛФ – лекарственная форма; МНН – международное непатентованное наименование; НДС – налог на добавленную стоимость; п/к – подкожный; РКИ – рандомизированное контролируемое исследование; рчЭПО – рекомбинантный человеческий эритропоэтин; ССЗ – средства стимуляторы эритропоэза; ХБП – хроническая болезнь почек; ХПН – хроническая почечная недостаточность; ЭПО – эпоэтин

INTRODUCTION

Currently, there is an acute issue of the high prevalence of chronic kidney disease in the general population. It has been notified that on average, it can reach 13.4%, and in terms of coverage, it is comparable to arterial hypertension and diabetes mellitus. Chronic kidney disease (CKD) is often associated with

nephrogenic anemia, which complicates the course of CKD and tends to worsen due to the CKD progresses. In modern clinical practice, anemia of the renal origin is a frequent complication and is observed with a decrease in creatinine clearance to 40–60 ml/min. It is widespread in all types of renal replacement therapy, but is especially pronounced in dialysis pa-

tients (in the absence of treatment, the hemoglobin level below 10 g/dl can be observed in 90% of dialysis patients)^{1,2}. Anemia is associated with a deterioration in patients' quality of life (QoL), an increase in cardiovascular complications and the frequency of CKD patients' hospitalizations³. In the pathogenesis of nephrogenic anemia, a key factor is a deficiency in the production of endogenous erythropoietin in the kidneys. In clinical practice, for the treatment of nephrogenic anemia, preparations of recombinant human erythropoietin (r-HuEPO) are widely used. Timely correction of anemia to the recommended targets can improve the effectiveness of treatment in general and reduce the incidence of cardiovascular and infectious complications in CKD⁴ patients.

According to the national Russian Recommendations, the diagnosis of nephrogenic anemia is detected in CKD patients when the hemoglobin concentration drops below the average level by 2 standard deviations, taking into account the age and gender. Anemia in patients on renal replacement therapy (RRT) is considered as a decrease in hemoglobin lower than 11.5 g/dL in women and 13.5 g/dL in men, as well as lower than 12.0 g/dL in people over 70 years⁵. Currently, according to the majority of recommendations, the aim of treatment is to achieve a hemoglobin level of 10–12 g/dL both at the pre-dialysis stages of CKD, in dialysis patients and after kidney transplantation. International KDIGO 2012⁶ guidelines and Russian Clinical Guidelines for CKD⁷ prescribe starting treatment with r-HuEPO only when the hemoglobin level drops to 9–10 g/dL, while the upper limit for most patients is determined at 11.5 g/dL. Achieving higher Hb targets is not associated with significantly greater clinical effectiveness in terms of the risks of death or cardiovascular complications; on the contrary, it may be associated with a greater risk of adverse outcomes (increased blood pressure, vascular access thrombosis). Thus, the use of the lowest possible doses of erythropoiesis stimulating agents (ESAs) for the treatment of nephrogenic anemia in CKD patients makes it possible to avoid the risks of unfavorable vascular outcomes, as well as improve their quality of life (QoL) [1], eliminate anemic syndrome and reduce the frequency of blood transfusions in patients on hemodialysis⁸.

It is generally accepted that the incidence of side

effects such as seizures, headaches, increased need for heparin during hemodialysis, impaired dialyzer clearance, and hyperkalemia does not increase significantly with the use of ESA. One of the frequent and serious undesirable effects of r-HuEPO therapy is the occurrence or progression of arterial hypertension – up to 30% of patients may need to increase the doses of antihypertensive drugs. When treating patients with CKD complicated by diabetes mellitus, malignant neoplasms, strokes, a non-ischemic heart disease or a peripheral vascular disease, it is recommended to prescribe ESA with caution, the target hemoglobin range can be reduced to 10–11 g/dL.

In Russian databases, there is a number of published works on the pharmacoeconomic analysis of the use of short, intermediate and long-acting epoetins. The authors were most interested in the treatment of nephrogenic anemia in CKD patients undergoing substitution therapy in the system of domestic health care. Publication by R.I. Yagudina et al., 2009 [2], is devoted to assessing the effectiveness of EPO alpha (Eprex), EPO beta (Recormon) and DA (Aranesp) in dialysis and pre-dialysis patients. In the publication by M.V. Avksentieva, a comparative analysis of the costs of therapy with DA and EPO alfa (the original drug Eprex) was carried out [3]. The work by Krysanov I.S. et al., 2016 [4] is devoted to a comparative assessment of the use of EPO alfa (Eprex, Eralfon), DA (Aranesp) and long-acting EPO (Mircera) in dialysis patients in real clinical practice. These studies show high costs of managing such patients, but they were carried out in the period of 2009–2016, and not all studies reflect the investigated medicinal products, which determines the relevance of this study.

THE AIM of this study is to conduct a comparative cost-effectiveness analysis of short-, intermediate- and long-acting r-HuEPOs prescribed for the correction of nephrogenic anemia in adult patients with an end-stage chronic kidney disease requiring dialysis therapy.

MATERIALS AND METHODS

The objects of the study were:

1. Short-acting r-HuEPO – epoetin alfa (EPO alfa). Trade name: Eralfon®, release form: 2500 µg syringe, the holder of the Marketing authorization (LSR-006663/08) – CJSC PharmFirma Sotex, Russia;
2. Intermediate-acting rhEPO – darbepoetin alfa (DA). Trade name: Aranesp®, release forms: 20 µg, 30 µg syringe, the holder of the Marketing authorization (LSR-001710/07) – Amgen, the Netherlands. Trade name: Darbestim®, release forms: 20 µg, 30 µg, 40 µg syringe, the holder of the Marketing authorization (LP-005411) – CJSC "Biocad", Russia;
3. Long-acting r-HuEPO – methoxy polyethylene glycol – epoetin beta. Trade name: Mircera®, release forms: 50 µg, 75 µg, 100 µg syringe, the holder of the Marketing authorization (LSR-002182/08) – F. Hoffmann-La Roche Ltd., Switzerland.

The primary source of the data were clinical guidelines KDIGO 2012, updated Russian National Guidelines

¹ Clinical guidelines. Chronic kidney disease. 2019. 169 p. Russian

² Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed. Moscow, 2014. 34 p. Russian

³ Clinical practical recommendations KDIGO on anemia in chronic kidney disease 2012. Nephrology and dialysis. 2013; 15(1): 14-53. Russian

⁴ Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 edition.

⁵ Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed.

⁶ Clinical practical recommendations KDIGO on anemia in chronic kidney disease, 2012.

⁷ Clinical guidelines. Chronic kidney disease. 2019.

⁸ Ibid.

for the diagnosis and treatment of anemia in chronic kidney disease, Federal Clinical Guidelines for the diagnosis and treatment of anemia in chronic kidney disease, National Guidelines for CKD, as well as a retrospective, multicenter observational study (Choi P, 2013) [5].

The search and selection of literature data on the effectiveness and safety of r-HuEPO for the nephrogenic anemia treatment in adult dialysis patients was carried out in the available medical databases: PubMed database, Cochrane Library. The keywords were: epoetin [All Fields] AND CKD [All Fields] AND ("renal dialysis" [MeSH Terms] OR ("renal" [All Fields] AND "dialysis" [All Fields]) OR "renal dialysis" [All Fields]] OR "dialysis" [All Fields] OR "dialysis" [MeSH Terms]]. The search depth was 15 years – January 2006 – July 2020, the studies carried out in 2005 and earlier, were excluded from the further analysis.

In the selection of works, the preference was given to meta-analyses, randomized controlled trials (RCTs), systematic reviews, then to clinical trials (CTs) without randomization. The following studies were excluded from the analysis: animal studies; the studies devoted to the research of the dosage form of the drug; CI 1–2 phases; research conducted in pediatric and/or geriatric practice; CTs in the cohort of pre-dialysis patients, CTs in the cohort of patients with concomitant diseases: cancer, diabetes, HIV infection, etc.

In the PubMed database, 140 publications were found, in the Cochrane Library database they were 4. For the pharmacoeconomic analysis, taking into account the inclusion and exclusion criteria, 12 publications were selected (Fig. 1). Six studies (4 meta-analyses, 1 systematic review, 1 RCT) were used to assess the effectiveness and

safety of therapy: the data from the World Health Organization report⁹ and 5 peer-reviewed publications [6-10] the data from the pharmacoeconomic study [11] were adapted to the conditions of the domestic health care system and used in conducting a pharmacoeconomic study at the national level, 5 CTs [5, 12–15] served as a source of data for calculating equivalent doses of the studied drugs.

Russian and foreign Clinical guidelines recommend a 2-stage treatment of nephrogenic anemia. The first phase is the correction of anemia, the aim of which is to achieve a lower limit of the target hemoglobin level. In phase 1 of treatment, the starting r-HuEPO¹⁰ doses are usually used. The second phase is maintenance therapy with the EPO doses, which are 20-30% lower than the starting ones¹¹. Taking into account that the selection of doses and the duration of phase 1 are more dependent on the individual characteristics of a patient, the cost-effectiveness analysis was carried out for the maintenance phase of treatment at the rate of 1 year of continuous therapy. To determine the standard dosage regimens for EPO drugs at the stage of maintenance therapy (Table 1), the instructions for medications, international and National Clinical Guidelines¹² for the treatment of dialysis patients with anemia in the CKD¹³, were analyzed.

⁹ WHO EML 2016-2017 – Application for erythropoietin-stimulating agents (erythropoietin type blood factors). WHO EML 2016–2017 – Erythropoietin-stimulating agents December, 2016.

¹⁰ Clinical guidelines. Chronic kidney disease. 2019.

¹¹ Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed.

¹² Clinical practical recommendations KDIGO on anemia in chronic kidney disease, 2012.

¹³ Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed.

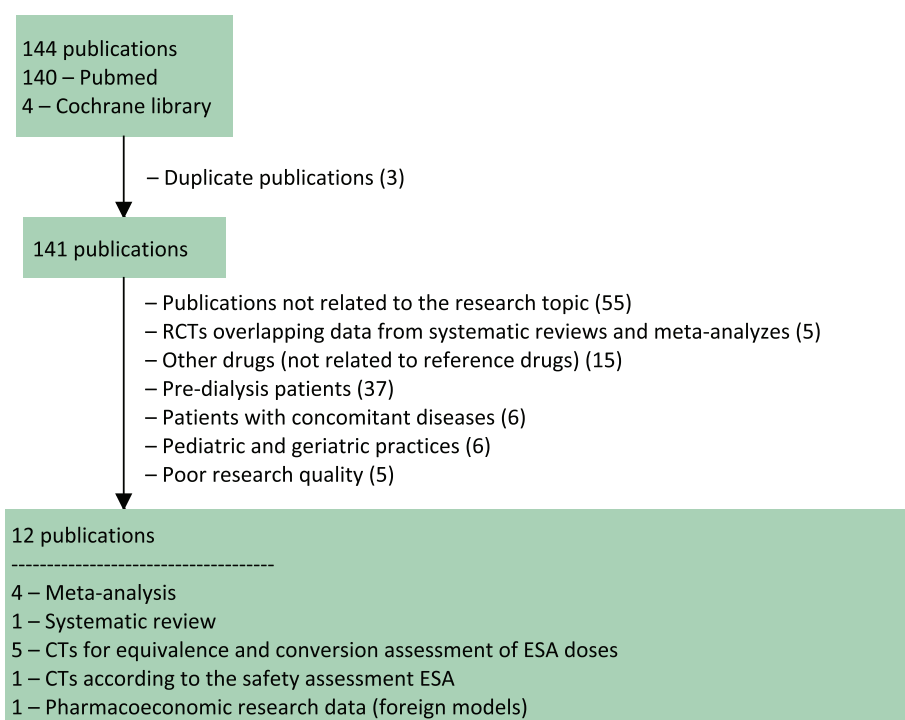


Figure 1 – Results of data selection for cost-effectiveness analysis

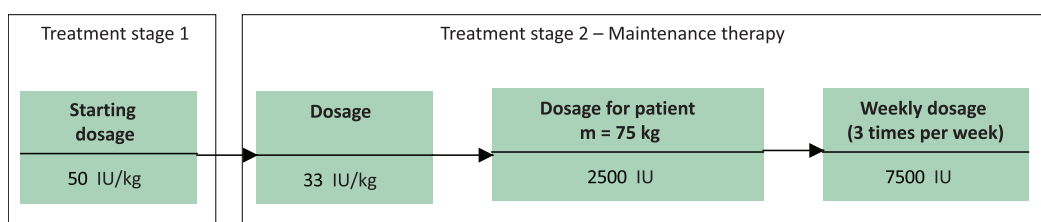


Figure 2 – Scheme of maintenance therapy with epoetin alfa

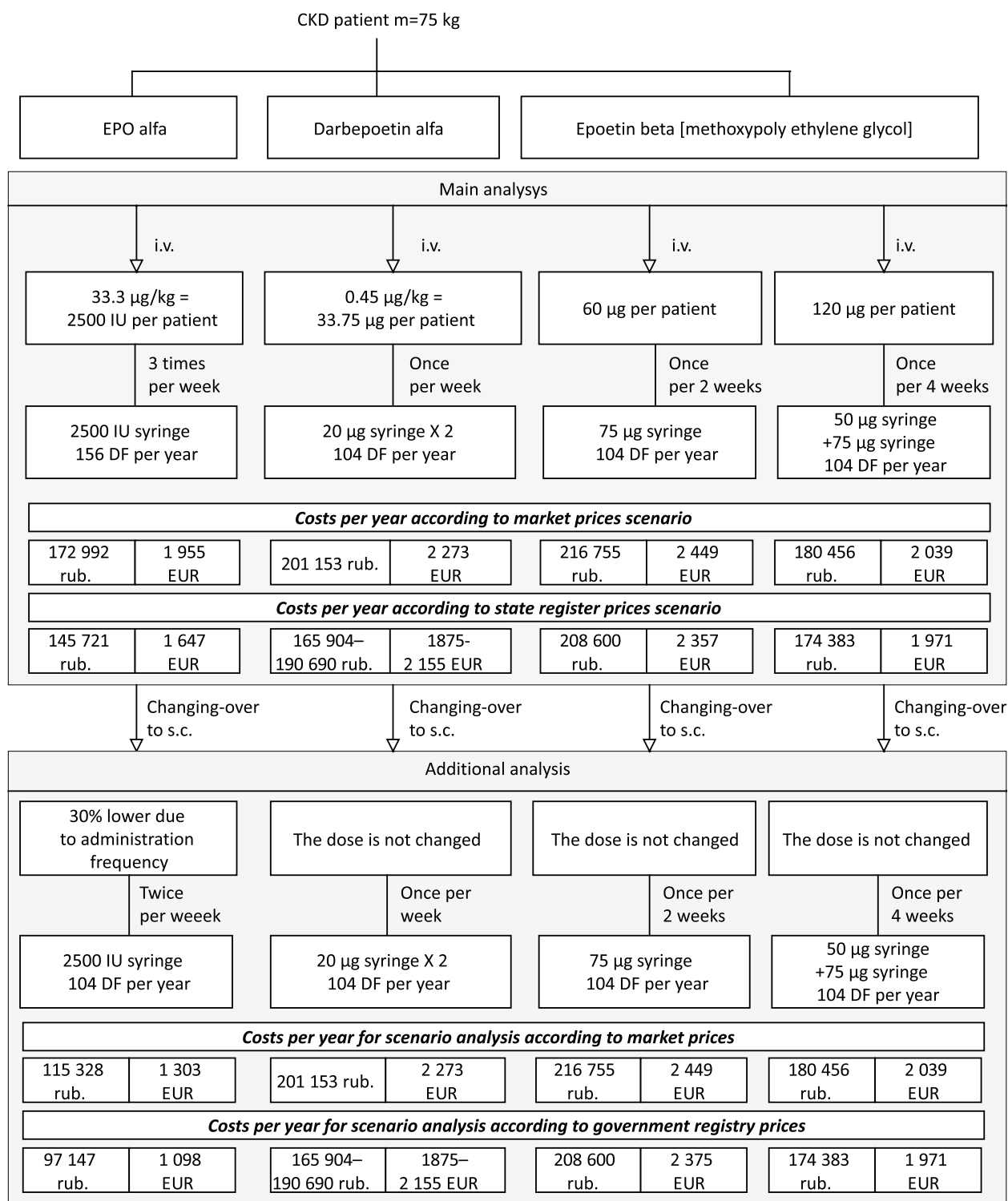


Figure 3 – Costs analysis for ESAs subcutaneous administration

Table 1 – Algorithms of maintenance drug therapy for nephrogenic anemia in target cohort of patients

International non-propriety name	Mode of administration	Maintenance therapy scheme
EPO alpha	i.v.	33.3 IU/kg – 3 times per week
	s.c.	reducing administration frequency to once-twice per week (weekly doses – 30% lower than in i.v. administration)
DA	i.v.	0.45 µg/kg – once per week
	s.c.	0.90 µg/kg – once per 2 weeks
Methoxy polyethylene glycol – epoetin beta	i.v.	When changing-over from other r-HuEPOs if the previous weekly dose was: <8000 IU per week EPO alpha
	s.c.	<40 µg/week DA
		60 µg – once per 2 weeks 120 µg – once per 4 weeks

Table 2 – Data of tender purchases of drugs – stimulants of erythropoiesis (01.01.2020-06.07.2020), top prices of the state drugs register

Trade name	INN	Dose	Qty. in pack	Price per unit, rub.	Price for 1 DF (syringe), rub.
Scenario 1 – Calculation at real pharmaceutical market prices					
Eralfon	EPO alpha	2500 IU	6	6 653.51	1 108.92
Aranesp	DA	20 µg	1	1 934.16	1 934.16
		30 µg	1	3 289.00	3 289.00
Mircera	EPO beta [methoxypoly ethylene glycol]	50 µg	1	5 544.48	5 544.48
		75 µg	1	8 336.74	8 336.74
		100 µg	1	10 222.74	10 222.74
Scenario 2 – Calculation at state register prices					
Eralfon	EPO alpha	2500ME	6	5 095.14	849.19 (934.11 with VAT)
Aranesp	DA	20 µg	1	1 666.87	1 666.87 (1 833.56 with VAT)
		30 µg	1	2 502.22	2 502.22 (2 752.44 with VAT)
Darbestim	DA	20 µg	1	1450.21	1450.21 (1 595.23 with VAT)
			4	5800.83	1450.21 (1 595.23 with VAT)
		30 µg	1	2176.51	2176.51 (2 394.16 with VAT)
			4	8706.02	2176.51 (2 394.16 with VAT)
		40 µg		Dosage (not included in VED list)	
Mircera	EPO beta [methoxypoly ethylene glycol]	50 µg	1	4 900.93	4 900.93 (5 391.02 with VAT)
		75 µg	1	7 293.72	7 293.72 (8 023.09 with VAT)
		100 µg	1	9 293.47	9 293.47 (10 222.82 with VAT)

Note: average price for a pack in pharmaceutical market – median for 1–2 qtrs., 2020; * 1 pack price is indicated in brackets at state register price including VAT

Table 3 – Equivalent doses of EPO

Initial data	Converting coefficient	Data source	Source characteristics	Equivalent dosage per week.	Equivalent DF (amp., syringe)
Clinical trials					
Short-acting EPO → Darbepoetin alfa					
<8000 IU per week	---	Sulowicz W et al, 2007 [15]	Controlled, open-label, randomized CT with parallel groups, phase 3, assessment of EPO effectiveness and safety in CKD patients, n = 572	<40 µg	20 µg * 2 DF per week 30 µg per week
7500 IU per week	200:1	Kuwahara M et al, 2015 [13]	Prospective CT, evaluation of EPO effectiveness in CKD patients over 144 weeks long, n = 297	37.5 µg per week	20 µg * 2 DF per week
7500 IU per week	206:1	Fuller DS et al, 2018 [17]	Data analysis of prospective cohort CT "DOPPS", phase 5 data for 9 countries*, 164 medical organizations, n = 3 281, CKD dialysis patients	36.4 µg per week	20 µg * 2 DF per week

Initial data	Converting coefficient	Data source	Source characteristics	Equivalent dosage per week.	Equivalent DF (amp., syringe)
7500 IU per week	222:1	Raymond CB et al, 2008 [14]	Retrospective analysis of real practice (Canada) in Manitoba Renal Program framework, n = 295, peritoneal dialysis	33.8 µg per week	20 µg * 2 DF per week
7500 IU per week	244:1	Raymond CB et al, 2008 [14]	Retrospective analysis of real practice (Canada) in Manitoba Renal Program framework, n = 1086, hemodialysis	30.7 µg per week	30 µg per week (assumption)
Short-acting EPO → Methoxy polyethylene glycol – epoetin beta					
7500 IU per week	255:1	Fuller DS et al, 2018 [17]	Data analysis of prospective cohort CT "DOPPS", phase 5 data for 9 countries *, 164 medical organizations, n = 3 281, CKD dialysis patients	59 µg per 2 weeks 118 µg per 4 weeks	75 µg * 2 DF per month 75+50 µg per month
Darbepoetin alfa → Methoxy polyethylene glycol – epoetin beta					
24.1 µg per week	1:1.17	Choi P et al, 2013 [5]	Retrospective multicenter research, study and determination of equivalence coefficient of weighted average EPO doses in CKD dialysis patients, n = 302	28.6 µg per week 57.2 µg per 2 weeks 114.4 µg per 4 weeks	75 µg * 2 DF per month 75+50 µg per month
30.7 µg per week	1:0.93	Kuwahara M et al, 2015 [13]	Prospective CT, evaluation of EPO effectiveness in CKD patients over 144 weeks long, n = 297	28.6 µg per week 57.2 µg per 2 weeks 114.4 µg per 4 weeks	75 µg * 2 DF per month 75+50 µg per month
<40 µg	–	Sulowicz W et al, 2007 [15]	Controlled, open-label, randomized CT with parallel groups, phase 3, evaluation of EPO effectiveness and safety in CKD patients, n = 572	60 µg per 2 weeks 120 µg per month	75 µg * 2 DF per month 75+50 µg per month
Methoxy polyethylene glycol – epoetin beta → Darbepoetin alfa					
118 µg per 4 weeks	0.89: 1	Fuller DS et al, 2018 [17]	Data analysis of prospective cohort CT "DOPPS", phase 5 data for 9 countries*, 164 medical organizations, CKD dialysis patients, n = 3 281	>26.3 µg per week	30 µg
27.4 mg per week	1.06:1	Donck J et al, 2014 [12]	Multicenter, observational CT, search for equivalent EPO doses in real practice in CKD hemodialysis patients, n = 1027	25.6 µg per week	30 µg
International and Russian recommendations					
Short-acting EPO → Darbepoetin alfa					
7500 IU per week	200:1	KDIGO 2012 ¹⁴	KDIGO Clinical Practice Guidelines for Anemia in Chronic Kidney Disease 2012	37.5 µg per week	20 µg * 2 DF per week
7500 IU per week	200:1	Russian Recommendations 2014 ¹⁵	Updated Russian national guidelines for anemia diagnosis and treatment of chronic kidney disease, revised in 2014	37.5 µg per week	20 µg * 2 DF per week
7500 IU per week	200:1	Instructions on drugs	Official instructions on medicinal products approved by the Ministry of Health (grls.rosminzdrav.ru)	37.5 µg per week	20 µg * 2 DF per week
7500 IU per week	240:1	Federal Recommendations 2014 ¹⁶	Federal clinical guidelines for anemia diagnosis and treatment in chronic kidney failure, 2014	31.25 µg per week	20 µg * 2 DF per week 30 µg per week (assumption)
Short-acting EPO → Methoxy polyethylene glycol – epoetin beta					
<8000 IU per week	---	Instructions on drugs	Official instructions on medicinal products approved by the Ministry of Health (grls.rosminzdrav.ru)	60 µg per 2 weeks 120 µg per month	75 µg * 2 DF per month 75+50 µg per month
Darbepoetin alfa → Methoxy polyethylene glycol – epoetin beta					
<40 µg	---	Instructions on drugs	Official instructions on medicinal products approved by the Ministry of Health (grls.rosminzdrav.ru)	60 µg per 2 weeks 120 µg per month	75 µg * 2 DF per month 75+50 µg per month

Note: * countries included in the analysis: Belgium, France, Germany, Italy, Russia, Spain, Sweden, Turkey, United Kingdom

¹⁴ Clinical practical recommendations KDIGO on anemia in chronic kidney disease 2012.

¹⁵ Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed.

¹⁶ Ibid.

Table 4 – Number of annual i.v. doses of r-HuEPO for maintenance therapy – main analysis

INN	Average dosage per m = 75 kg	Frequency of administration	Equivalent DF	Qty of doses	Qty of DFs
EPO alpha	2500 IU	3 times per week	2500 IU	156	156
DA	37.5 µg	once per week	20+20 µg	52	104
Methoxy polyethylene glycol – epoetin beta	60 µg	once per 2 weeks	75 µg	26	26
	120 µg	once per 4 weeks	75+50 µg	13	26

Table 5 – Analysis of EPO cost minimization in i.v. administration

Medicinal product	INN	Qty of DF per year	Cost of 1 DF, rub./euro	Costs per year, rub. (euro)	Differences in chang- ing-over to EPO alpha	
					rub. / euro	%
Scenario 1 – Calculation at real pharmaceutical market prices						
Eralfon 2500 IU	Epoetin alfa	156	1 108.92 / 12.53 €	172 992 / 1 955 €	---	---
Aranesp 20 µg	Darbepoetin alfa	104	1 934.16 / 21.85 €	201 153 / 2 273 €	- 28 161 / - 318 €	-14
Mircera 75 µg	Epoetin beta [methoxypoly ethylene glycol]	26	8 336.74 / 94.20 €	216 755 / 2 449 €	- 43 763 / - 494 €	-20
Mircera 50 µg + 75 µg		13	5 544.48 / 62.65 €	180 456 / 2 039 €	- 7 464 / -84 €	-4
		13	8 336.74 / 94.20 €			
Scenario 1 – Calculation at the prices of the state register						
Eralfon 2500 IU	Epoetin alfa	156	934.11 / 10.55 €	145 721 /1 647 €	---	---
Aranesp 20 µg	Darbepoetin alfa	104	1 833.56 / 20.72 €	190 690 /2 155 €	- 44 969 / -508 €	-24
Darbestim 20 µg	Darbepoetin alfa	104	1 595.23 / 18.03 €	165 904 /1 875 €	- 20 183 / - 228 €	-12
Mircera 75 µg	Methoxy polyethylene glycol – epoetin beta	26	8 023.09 / 90.66 €	208 600 /2 357 €	- 62 879 / -710 €	-30
Mircera 50 µg + 75 µg		13	5 391.02 /60.92 €	174 383 / 1 971 €	- 28 662 / - 324 €	-16
		13	8 023.09 /90.66 €			

According to the recommendations of KDIGO 2012, in a hemodialysis patient, the most effective frequency of short-acting ESA – EPO alfa administration is 3 times per week. Among prolonged-release drugs, DA is usually started with a dose of 0.45 µg/kg body weight once per week subcutaneously (s. c.) or intravenously (i. v.) for dialysis patients. In the maintenance phase of treatment, DA continues to be administered once a week, or the administration is changed-over to once per two weeks, increasing the initial dose twice, the most optimal dosing regimen for methoxy polyethylene glycol – epoetin beta is the administration of the drug once per 4 weeks. In patients not receiving dialysis treatment or receiving treatment with peritoneal dialysis, the subcutaneous administration is preferable, and in hemodialysis patients it is intravenous. It is important to notify that for short-acting ESA, the effectiveness of the subcutaneous administration in hemodialysis patients is higher than that of

the intravenous administration, which makes it possible to reduce the weekly dose of the injected drug by 30%, while for long-term ESA, the effectiveness of subcutaneous and intravenous administrations is equivalent.

The study time horizon was 1 year of continuous erythropoietins therapy. Since modern approaches to the anemia treatment often involve the beginning of anemia correction at the pre-dialysis stage of CKD treatment, when calculating the costs for long-acting epoetin beta, the study included dialysis patients and the ones who had been treated with EPO preparations in the volume equivalent to the average maintenance dose of EPO alfa or DA (<8000 IU per week and <40 µg per week, respectively) 1, 3.

The costs were calculated according to two scenarios: according to the data of tender purchases of the investigated drugs in 2020 (01.01.2020-06.07.2020), and according to the maximum selling prices of the manu-

facturer (including value added tax (VAT)), since all the investigated dosage forms are included in the current list of "Vital and Essential Drugs" (VED).

According to the instructions on the medicinal product, pre-filled syringes are used for only one injection, and therefore, when calculating the costs, it was taken into account that if it was necessary to administer a part of the dose to one patient, the remainder of the unclaimed medicinal product in the syringe was disposed of and not used. In this regard, for the pharmacoeconomic analysis, the price for 1 dosage form (DF) (syringe) was calculated (Table 2). The average price per unit in the pharmaceutical market was determined as the median among all prices of completed tenders at the time of the study (the main analysis is Scenario 1) or as the price of the state register + value added tax (VAT – 10%) (the main analysis is Scenario 2).

For darbepoetin with the trade name Darbestim, which is a reproduced drug, there were no sales data for the analyzed period (01.01.2020-06.07.2020). From 02.09.2020 the drug was included in the VED list; therefore, it was calculated at the state register prices. When converting the costs in euros, the average annual rate of the euro in 2021 was used – 1 euro = 88.5 rubles.

RESULTS

The meta-analysis by Amato, 2017 [6] of 30 studies results covered the sample of 7843 CKD patients, 21 studies of which included hemodialysis or peritoneal dialysis patients. The results showed the equal effectiveness and safety of epoetin alfa, DA and methoxy polyethylene glycol – epoetin beta. However, DA was statistically significantly superior to EPO alfa in reducing the number of transfusions. The meta-analysis by Saglimbene, 2017 [9] included 27 publications (n = 5410): 7 – pre-dialysis patients, 19 – dialysis patients, 1 – a patient requiring kidney transplantation. It was found out that methoxy polyethylene glycol – epoetin beta in various dosages significantly little differs in terms of safety and effectiveness profiles in comparison with EPO alfa and DA. The meta-analysis by Palmer, 2014 [7] included 21 publications (n = 8328). A comparative analysis of DA and placebo was carried out in 1 publication; a comparison of DA and epoetin alfa – in 16; DA and methoxy polyethylene glycol – epoetin beta were compared in 4 publications; DA in different dosage modes – in 3 works; the analysis of various methods of DA administration (i.v. or s.c.) – in 4 publications. It was revealed that DA reduced the number of transfusions in CKD patients at stages 3–5, but it did not affect the mortality and patients' QoL, and its overall effectiveness was comparable to its analogs (EPO alfa, methoxy polyethylene glycol – epoetin beta). Another meta-analysis by Palmer, 2014 [8], which included 56 publications and 15596 patients, also

found out no differences in the effectiveness and safety of EPO alfa versus DA and methoxy polyethylene glycol – epoetin beta. A systematic review by Wilhelm-Leen, 2014 [16] also showed that DA is equivalent to epoetin alfa in terms of effectiveness and safety. A multicenter randomized controlled open-label study carried out by Locatelli, 2019 [10], investigated the safety of methoxy polyethylene glycol – epoetin beta in comparison with EPO alpha, EPO beta and DA in 2818 CKD patients (dialysis and predialysis patients) with a history of anemia. The researchers found out that in the target cohort of patients, taking methoxy polyethylene glycol – epoetin beta once a month is no worse than taking analog drugs in terms of adverse cardiovascular complications or mortality from all causes. Thus, based on the analyzed data of meta-analyses, a systematic review and RCTs, a conclusion was made about the comparable effectiveness in achieving the target values of Hb and the safety of EPO alfa relative to DA and methoxy polyethylene glycol – epoetin beta.

At the next stage of the study, the dosage of EPO alfa for the maintenance therapy stage according to the instructions on the drug was calculated. Thus, for maintenance therapy, it is recommended to reduce the starting dose of 50 IU / kg by 1.5 times (Fig. 2).

A number of studies [5, 12–15, 17] devoted to the calculation of the coefficients for converting EPO doses into equivalent ones, have been analyzed. The results obtained (Table 3) made it possible to substantiate the choice of equivalent doses of EPO preparations of various generations for an average patient with a body weight of 75 kg.

It should be notified that when converting short-acting EPO to DA, the dose conversion factors varied from 200: 1 to 244: 1. When converting short-acting EPO doses to methoxy polyethylene glycol – epoetin beta, the conversion factor was 255: 1, or it was indicated that a weekly dose of epoetin alpha less than 8000 µg is equivalent to 60 µg/once per 2 weeks or 120 µg/once per 4 weeks. When choosing equivalent doses, the emphasis was made on the coefficients recommended by international and Russian clinical recommendations and guidelines, as well as the conversion rates used in real clinical practice [17]. One of the limitations of the model is also the fact that in real clinical practice the maintenance doses that CKD dialysis patients with anemia can receive, vary significantly and are more dependent on the individual characteristics of patients.

Thus, the equivalent ESA doses for the main clinical and economic study were determined and scientifically substantiated:

- Epoetin alfa – 2500 IU * 3 times per week (the intravenous administration, according to the instructions and clinical guidelines);

• Darbepoetin alfa – 20 + 20 µg (30.7–40 µg) * once per week (the dosage of 30 µg/week is included in the sensitivity analysis);

• Epoetin methoxy polyethylene glycol – epoetin beta – 75 µg (57.2–60 µg) * once per 2 weeks or 75 + 50 µg (114.4–120 µg) * once per 4 weeks. At the same time, in a number of studies it is notified that the dose of long-acting EPO in dialysis patients can vary from 100–200 µg per 4 weeks (100 µg (n = 585) [18], 119 µg (n = 63) [19], 100–200 µg (n = 60) [20], 115 µg (n = 184) [21], 153 µg (n = 3281) [17]). In the present study, the calculations were performed for patients receiving high doses of long-acting EPO equivalent to the doses according to clinical guidelines.

Table 4 shows the results of calculating the number of intravenous ESA injections per year per 1 CKD patient at the end-stage (with an average body weight of 75 kg).

Thus, on average, the frequency of injections of short-acting epoetins is 156 per year, darbepoetin alfa – 52 injections per year, methoxy polyethylene glycol – epoetin beta – 13 injections or 26 injections per year for once per 4 weeks and once per 2 weeks, respectively.

The results of the main cost-effectiveness analysis of cost minimization for drugs used i. v., are presented in Table 5.

It was revealed that when calculated at tender prices in the public procurement system (according to the data of 2020), the costs for treating anemia with epoetin alfa 2500 IU will be 172,992 rubles (€ 1,955) per patient per year. In comparison with DA, the use of epoetin alfa will reduce costs by 28,161 rubles (318 €) per year per patient (14%). Compared to methoxy polyethylene glycol – epoetin beta, epoetin alfa can save from 4 to 20%.

When calculated at the state register prices, the differences in costs will be more significant – compared to DA, the costs will be lower by a quarter (–24%), compared to methoxy polyethylene glycol – epoetin beta, and the differences in costs varied from –16% to –30%.

It should be notified that in dialysis patients, short-acting EPO can also be used subcutaneously, which makes it possible to reduce the administered dose and, accordingly, the cost of drugs by 20–30%. Fig. 3 below shows the results of the cost minimization analysis of the study drugs in the comparative aspect when administered s / c.

Since to achieve a similar effect, in s.c. EPO alfa administration a patient needs the dose up to 30% lower than in i.v. administration this makes it possible to use a lower frequency of the drug administration (twice per week). In its turn, it makes it possible to reduce the cost of pharmacotherapy by a third – from 172,992 rubles up to 115, 328 rubles (from 1,955 € to 1,303 €), or from 145,721 rubles up to 97 147 rubles (from € 1,647 to € 1,098) for market prices and state register prices,

respectively. Prolonged action ESAs can also be used s/c, however, no adjustment of the administered dose is made.

Thus, when changing-over from i.v. to s. c. administration of the studied ESAs, the savings in choosing epoetin alfa for the correction of nephrogenic anemia can reach 50% (36–47% and 44–53% for market prices and state register prices, respectively).

DISCUSSION

According to the Russian clinical guidelines on the treatment of CKD, meta-analyses [6–9], clinical [10] and retrospective studies [17], it can be stated with a high evidence level that no significant differences in the effectiveness of different ESAs for the correction of anemia have been revealed. No significant differences have been either shown between original and biosimilar epoetins [6, 22, 23]. At the same time, there are cases of an increase in the partial erythrocytes aplasia in the use of some locally produced epoetins (in Asia and Latin America). These kinds of drug production should be accompanied by strict protocols for the approval of biosimilar drugs by the regulatory authorities of some countries, including the RF¹⁷. The use of CKD makes it possible to achieve the target hemoglobin values (100–120 mg/ml) with maintenance therapy for 6 months or more in more than 80% of patients [24].

This research made it possible to update the previously obtained data from a similar study by Krysanov, 2019 [25]. The previous study included a marketing analysis of prices for 3 quarters of 2018 (01.01.2018–31.09.2018). In this study, the prices for medicines were updated according to the tenders carried out in 2020 (01.01.2020–06.07.2020). In connection with the mandatory re-registration of the manufacturers' maximum selling prices for the drugs included in the VED list, an additional analysis of the treatment costs was carried out and calculated on the basis of the state register prices.

The updated results also indicate that epoetin alfa (Eralfon®) has an economic advantage relative to darbepoetin alfa (Aranesp®) and methoxy polyethylene glycol – epoetin beta (Mircera®) in both the intravenous and subcutaneous administrations of the investigated drugs when used in equivalent maintenance doses in adult patients who have previously received EPO therapy, with equal effectiveness and safety. It should be notified that the intravenous administration is preferable for dialysis patients; however, changing-over to the subcutaneous administration of the drug can also be considered for such a cohort of patients. For short-acting ESAs, the effectiveness of the subcutaneous administration is higher than intravenous, which makes it possible to reduce

¹⁷ Clinical guidelines. Chronic kidney disease. 2019.

the frequency of the drugs administration in this group (twice per week), reduce the dose and the cost of drug therapy in relation to long-term ESAs by 30%. Herewith, the effectiveness in the subcutaneous and intravenous administrations appears to be equal at the investigated dosage frequencies¹⁸. It should be notified that in real clinical practice, the subcutaneous method of administration could hardly be suitable to all patients due to its high painfulness or other clinical features.

The sensitivity analysis of the data obtained in this study, to a change in the dosing regimen of darbepoetin alfa showed that with a decrease in the weekly dose of DA with 2 DF* 20 µg per week up to 30 µg (1 DF* 30 µg) ([8, 10]), the per year costs for therapy with epoetin alfa will be insignificantly higher than with darbepoetin. In comparison with INN Aranesp, the per year cost of therapy with epoetin alfa is 1% higher (172 992 rubles and 171,028 rubles, or 1,955 € and 1,933 €), or 2% (145,721 rubles and 143,127 rubles, or 1,647 € and 1,617 €) when calculated at market prices and the prices of the state register, respectively. In comparison with INN Darbestim 30 µg once a week, the cost of therapy with epoetin alfa per year is 17% higher (145,721 rubles and 124,496 rubles, or 1,647 € and 1,407 €) when calculated at the prices of the state register, i.e., the results of calculations with respect to reproduced DA are sensitive to changes in the dosage regimen. Thus, for a cohort of patients treated with DA in the weekly dose of 30 µg, the differences in the costs of the annual treatment in comparison with the original DA (1–2%) can be considered insignificant, and in comparison, with the reproduced drug – as significant (17%).

The sensitivity analysis of the data obtained to changing-over the dosage regimen of long-acting EPO from the 120 µg scheme once per 4 weeks (13 DFs per year) to 120 µg once a month (12 DFs per year) showed that the differences in costs varied within +4% to –9%. The costs depend on the method of price calculation – at real market prices or at VED prices, respectively. It should be notified that the calculations carried out, have limitations and reflect the costs in a comparative aspect in the patients administrated with high doses of Mircera (more than 100 µg per month). According to the conversion factors based on the international and Russian clinical guidelines, high doses of Mircera (more than 100 µg per month) are equivalent to the dosage regimen of epoetin alfa 2500 IU per patient * 3 times per week (7500 IU per week). A large-scale study conducted in 9 countries of the world, including the Russian Federation, shows that in real clinical practice, the average prescribed long-acting EPOs are close to high doses [17].

It should be notified that in the study by Krysanov et

al., 2016 [4], the use of short, intermediate and long-acting epoetins in hemodialysis patients with nephrogenic anemia, were also studied. The patients were administrated with different dosages of drugs depending on the target hemoglobin value. So, to achieve the index of 9 ± 1 g/dL, on average, the patients are administrated with epoetin alfa (biosimilar) 2,558 IU 3 times per week (7,674 IU – a weekly dose), DA 25 µg per week and long-acting EPO 161 µg per month. Under the assumption of neglecting the differences in the calculated values of single doses up to 6%, the above-listed doses will be equivalent: epoetin alfa syringe 2500 IU * 3 times per week – neglecting an error of 2%, darbepoetin syringe 30 µg * once per week – provided that a 30 µg syringe is used to achieve a single dose of 25 µg and methoxy polyethylene glycol – epoetin beta 100 + 50 µg * once per 4 weeks – neglecting an error of 6%. It should be notified that in the present study, EPO alpha 2,500 IU was comparable in price to DA 30 µg (the differences in costs did not exceed 2%) and more economical in comparison with methoxy polyethylene glycol – epoetin beta 75 + 50 µg. Thus, a conclusion can be made about comparable costs versus DA and the economic advantage versus long-acting EPO beta 100 + 50 µg, since the preparation with a dosage of 100 µg has a higher cost per pack in comparison with the release form of a lower dosage.

The obtained comparison results for the intravenous administration in the pair of EPO alpha and EPO beta long-acting* once per 2 weeks are insensitive to the price increases for EPO alpha (Eralfon®) up to +20%. The comparison results in the pair of EPO alfa and DA 20 µg per week are insensitive to the price increase up to +15%; EPO alpha remains an economically more profitable alternative. At the same time, in the pair of EPO alpha and methoxy polyethylene glycol – epoetin beta * once per 4 weeks, the results are sensitive up to 5% and the price increases for EPO alpha. The comparison results for the subcutaneous administration are insensitive to price increases for EPO alpha (it will be more economical even if prices rise by 50%).

The conclusions reached are relevant when calculating the cost per patient with an average body weight of 75 kg, and assuming that the number of dosage forms per injection is rounded to integers, the calculations may differ for other body weights.

CONCLUSION

Thus, with equal effectiveness and safety of the studied drugs, EPO alfa 2,500 IU 3 times per week administrated intravenously and subcutaneously, is a more economical drug technology in relation to darbepoetin 40 µg once per week and methoxy polyethylene glycol epoetin beta with the scheme both 60 µg twice per month and 120 µg once per month.

¹⁸ Clinical practical recommendations KDIGO on anemia in chronic kidney disease, 2012.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Ivan S. Krysanov – development of research design, article editing and final approval; Viktoria Yu. Ermakova – article editing, planning and developing the study design; Larisa B. Vaskova – article editing, planning and developing the study design; Marina V. Tiapkina – collecting material, data processing, writing and editing the article.

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