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

I.S. Krysanov1,2, V.Yu. Ermakova2,3, L.B. Vaskova3, M.V. Tiapkina3

1 Medical Institute of Continuing Education, Moscow State University of Food Production
11, Volokolamsk highway, Moscow, Russia, 125080
2 LLC “Institute of Clinical and Economic Expertise and Pharmacoeconomics”
Bld. 6, 21, Novomytishchinsky Ave., Mytishchi, Moscow region, Russia, 141008
3 Sechenov First Moscow State Medical University
Bld. 2, 8, Trubetskaya St., Moscow, Russia, 119991

E-mail: krysanov-ivan@mail.ru

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

И.С. Крысанов1,2, В.Ю. Ермакова2,3, Л.Б. Васькова3, М.В. Тяпкина3

1 Медицинский институт непрерывного образования Федерального государственного бюджетного образовательного учреждения высшего образования «Московский государственный университет пищевых производств» Министерства образования и науки Российской Федерации
125080, Россия, г. Москва, Волоколамское шоссе, 11

2 ООО «Институт клинико-экономической экспертизы и фармакоэкономики»
141008, Россия, Московская обл., г. Мытищи, Новомытищинский пр-кт, 21/6

3 Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет)
119991, Россия, г. Москва, ул. Трубецкая, д. 8, стр. 2

E-mail: krysanov-ivan@mail.ru

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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 клинико-экономическую оценку затрат на терапию нефрогенной анемии у взрослых пациентов, находящихся на диализе, рекомбинантными человеческими эритропоэтиками: 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 «минимизации затрат» для эквивалентных поддерживающих доз эпоэтинов для внутривенного и подкожного применения. Эквивалентные эпоэтину 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: дарбэпоэтина на 14–24% и эпоэтина бета (метоксиполиэтиленгликоль) – на 4–30%. Перевод больных на подкожное введение позволяет снизить недельную дозу эпоэтин 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 эритропоэтина; ССЭ – 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-
The primary aim of this study is to conduct a comparative assessment of the use 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 assessing the effectiveness of EPO alpha (Eprex), EPO beta (Recormon) and DA (Aranesp) in dialysis and pre-dialysis patients. 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 the investigation of the effectiveness of EPO alfa (Eprex) 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 — darbepeoin 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.
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 report8 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**

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144 publications
| 140 – Pubmed
| 4 – Cochrane library

  – Duplicate publications (3)

141 publications

  – Publications not related to the research topic (55)
  – RCTs overlapping data from systematic reviews and meta-analyses (5)
  – Other drugs (not related to reference drugs) (15)
  – Pre-dialysis patients (37)
  – Patients with comorbid diseases (6)
  – Pediatric and geriatric practices (6)
  – Poor research quality (5)

12 publications

  4 – Meta-analysis
  1 – Systematic review
  5 – CTs for equivalence and conversion assessment of ESA doses
  1 – CTs according to the safety assessment ESA
  1 – Pharmacoeconomic research data (foreign models)
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Figure 2 – Scheme of maintenance therapy with epoetin alfa

- CKD patient m=75 kg
- EPO alfa
- Darbepoetin alfa
- Epoetin beta [methoxypolyethylene glycol]

**Main analyses**

| i.v. | i.v. | i.v. | i.v. |
|------|------|------|------|
| 33.3 µg/kg = 2500 IU per patient | 0.45 µg/kg = 33.75 µg per patient | 60 µg per patient | 120 µg per patient |
| 3 times per week | Once per week | Once per 2 weeks | Once per 4 weeks |
| 2500 IU syringe 156 DF per year | 20 µg syringe X2 104 DF per year | 75 µg syringe 104 DF per year | 50 µg syringe +75 µg syringe 104 DF per year |

**Costs per year according to market prices scenario**

| 172 992 rub. | 1 955 EUR | 201 153 rub. | 2 273 EUR | 216 755 rub. | 2 449 EUR | 180 456 rub. | 2 039 EUR |

**Costs per year according to state register prices scenario**

| 145 721 rub. | 1 647 EUR | 165 904–190 690 rub. | 1875–2 155 EUR | 208 600 rub. | 2 357 EUR | 174 383 rub. | 1 971 EUR |

**Changing-over to s.c.**

**Additional analysis**

| 30% lower due to administration frequency | The dose is not changed | The dose is not changed | The dose is not changed |
| Twice per week | Once per week | Once per 2 weeks | Once per 4 weeks |
| 2500 IU syringe 104 DF per year | 20 µg syringe X2 104 DF per year | 75 µg syringe 104 DF per year | 50 µg syringe +75 µg syringe 104 DF per year |

**Costs per year for scenario analysis according to market prices**

| 115 328 rub. | 1 303 EUR | 201 153 rub. | 2 273 EUR | 216 755 rub. | 2 449 EUR | 180 456 rub. | 2 039 EUR |

**Costs per year for scenario analysis according to government registry prices**

| 97 147 rub. | 1 098 EUR | 165 904–190 690 rub. | 1875–2 155 EUR | 208 600 rub. | 2 375 EUR | 174 383 rub. | 1 971 EUR |

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 |
|                                  | i.v.                    | reducing administration frequency to once-twice per week (weekly doses – 30% lower than in i.v. administration) |
|                                  | s.c.                    | 0.45 µg/kg – once per week |
|                                  | s.c.                    | 0.90 µg/kg – once per 2 weeks |
| 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.                    | 60 µg – once per 2 weeks |
|                                  | s.c.                    | 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. |
|------------|-----|-----------|--------------|----------------------|-------------------------------|
| Eralfon    | EPO alpha | 2500 IU  | 6            | 6 653.51             | 1 108.92                      |
| Aranesp    | DA    | 20 µg    | 1            | 3 289.00             | 3 289.00                      |
| Mircera    | EPO beta [methoxypolyethylene 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

| Trade name | INN | Dose      | Qty. in pack | Price per unit, rub. | Price for 1 DF (syringe), rub. |
|------------|-----|-----------|--------------|----------------------|-------------------------------|
| Eralfon    | EPO alpha | 2500IE   | 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)   |
| Mircera    | EPO beta [methoxypolyethylene 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 |

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 | Data characteristics | Equivalent dosage per week | Equivalent DF (amp., syringe) |
|--------------|------------------------|-------------|----------------------|---------------------------|-------------------------------|
| <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 |

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
| 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) |
| 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 |
| 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 |
| 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 µg 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 → Methoxy polyethylene glycol – epoetin beta

| 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 → Darbepoetin alfa

| 7500 IU per week | 200:1 | 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 |

#### 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 |

### Note:

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

**Clinical practical recommendations KDIGO on anemia in chronic kidney disease 2012.
Updated Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease in the 2014 ed.
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 changing-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 / –14 |
| Mircera 75 µg | Epoetin beta [methoxypolyethylene glycol] | 26 | 8 336.74 / 94.20 € | 216 755 / 2 449 € | – 43 763 / – 494 € | –20 / –20 |
| Mircera 50 µg + 75 µg | Darbepoetin alfa | 13 | 5 544.48 / 62.65 € | 180 456 / 2 039 € | – 44 969 / – 508 € | –24 / –24 |
| 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 / –24 |
| Darbestim 20 µg | Darbepoetin alfa | 104 | 1 595.23 / 18.03 € | 165 904 / 1 875 € | – 20 183 / – 228 € | –12 / –12 |
| Mircera 75 µg | Methoxy polyethylene glycol – epoetin beta | 26 | 8 023.09 / 90.66 € | 208 600 / 2 357 € | – 62 879 / – 710 € | –30 / –30 |
| Mircera 50 µg + 75 µg | Methoxy polyethylene glycol – epoetin beta | 13 | 5 391.02 / 60.92 € | 174 383 / 1 971 € | – 28 662 / – 324 € | –16 / –16 |

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 alpha, 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 alpha 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 alfa 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 € 1,647 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 RF [17]. 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 darbeponetin alfa (Aranesp®) and methoxy polyethylene glycol – epoetin beta (Miricer®) 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 the cost of pharmacotherapy for dialysis patients.
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 estimated dosage frequencies. 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 administered 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 administered 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 alfa 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.
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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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AUTHORS

Ivan S. Krysanov – Candidate of Sciences (Pharmacy), Associate Professor, Head of the Pharmacy Course at the Medical Institute of Continuing Education, Moscow State University of Food Production; Head of the Department of Clinical and Economic Analysis, Institute of Clinical and Economic Expertise and Pharmacoeconomics. ORCID ID: 0000-0002-3541-1120. E-mail: krysanov-ivan@mail.ru

Viktoria Yu. Ermakova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Chemistry, Sechenov First Moscow State Medical University; General manager Institute of Clinical and Economic Expertise and Pharmacoeconomics. ORCID ID: 0000-0002-4822-7226. E-mail: ermakova.viktoriya.yurievna@mail.ru

Larisa B. Vaskova – Candidate of Sciences (Pharmacy), Associate Professor, Associate Professor of the Department of Organization and Economics of Pharmacy, Sechenov First Moscow State Medical University. ORCID ID: 0000-0003-3579-7577. E-mail: vaskovalb@mail.ru

Marina V. Tiapkina – Senior Lecturer of the Department of Organization and Economics of Pharmacy, Sechenov First Moscow State Medical University. ORCID ID: 0000-0002-6709-0317. E-mail: marina-tya@ro.ru