Renal Anemia Treatment with ESA in Hemodialysis Patients in Relation to Early versus Late Referral in Everyday Clinical Practice in Central and Eastern European Countries: Baseline Data

Jolanta Malyszko^a Maciej Drozd^b Agnieszka Zolkiewicz^c Boleslaw Rutkowski^d

^aDepartment of Nephrology and Transplantology, Medical University, Bialystok, ^bDepartment of Nephrology, Collegium Medicum, Jagiellonian University, Cracow, ^cRoche Pharmaceutical Company, Warsaw, and

^dDepartment of Nephrology, Transplantology and Internal Diseases, Medical University, Gdansk, Poland

Key Words

Chronic kidney disease · Renal anemia · Hemodialysis · Erythropoiesis-stimulating agents · Central and Eastern European countries

Abstract

The aim of the study was to collect retrospective data on renal anemia management, comorbidities and prospective data on 12-month standard care erythropoiesis-stimulating agent (ESA) therapy used in 398 hemodialyzed patients in selected Central and Eastern European countries (50 centers in 3 countries). Patients were divided into three groups according to ESA therapy start: group A-ESA (after start of hemodialysis, HD), B-ESA (within 3 months from start of HD), C-ESA (more than 3 months before HD). At the chronic kidney disease diagnosis, hemoglobin in all patients was 10.3 ± 2.3 g/dl; however, ferritin, iron, TSAT were within reference limits. Early ESA therapy (C) was administered to 10% of patients only. 47% of patients received ESA after start of dialysis. Before study, the mean weekly ESA dose in group C was statistically lower than in groups B and A ($p < 0.001$). At baseline visit, hemoglobin in group A patients was slightly lower than in group B and C patients ($p = 0.025$). In conclusion, in Central and Eastern European countries renal anemia therapy with ESA starts shortly before or after start of HD. This highlights

important differences in standard care in Eastern Europe. However, paradoxically, due to the tight reimbursement policy we foresee the clinical implications of the TREAT trial for the chronic kidney disease population.

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Introduction

Chronic kidney disease (CKD) is defined either as kidney damage or a glomerular filtration rate (GFR) of less than 60 ml/min for three months or more [1]. A normochromic, normocytic anemia is present in the majority of CKD patients, and begins during early renal insufficiency when the GFR falls below age-adjusted normal limits [2]. The diagnosis of anemia of CKD, so-called 'renal anemia', is usually made by excluding other potential causes of anemia in a patient with CKD, or in situations where there is moderate impairment of renal function (GFR 30–59 ml/min) and anemia is anticipated. In the setting of CKD, anemia has a number of potentially deleterious effects, including impairment of tissue oxygen delivery, increased cardiac output and left ventricular hypertrophy predisposing to congestive heart failure [3], cognitive decline, sexual dysfunction, and depression of immune responsiveness. The recent availability of erythropoietin

therapy has revolutionized management of anemia in CKD. It has significantly lessened the need to administer multiple blood transfusions and minimized the associated risks of transfusion, including alloimmunization, iron overload and transmission of infectious diseases. Administration of erythropoiesis-stimulating agents (ESA) to increase Hb concentrations from lower values to >10–11 g/dl significantly reduces the cardiovascular complications of renal anemia, and reduces the frequency of chronic heart failure and hospitalization among predialysis and dialysis-dependent patients [4, 5]. However, the recent CHOIR [6], CREATE [7] and TREAT [8] trials fail to demonstrate the reduction in cardiovascular complications in CKD patients in the high hemoglobin arm. Although mortality among CKD patients is high, recent studies have highlighted a substantial variability in outcome between centers and between countries [9, 10]. At present, the reason for differences in outcome between centers has not been fully explained. Only in the ORAMA study was a comparison between current management of renal anemia in both CKD and dialysis patients in Eastern and Western European countries performed [11]. The authors reported that baseline hemoglobin values in Eastern Europe were lower than in Western Europe. In the GAIN study [12] involving only hemodialysis (HD) subjects treated with any ESA for at least 12 weeks, and for 18 months with epoetin beta, there were regional differences between Balkan, Baltic, Eastern, Southern and Western Europe. However, these data were not analyzed. Due to the different reimbursement policies and reported lower hemoglobin levels in Eastern Europe as well as lower prevalence of diabetic nephropathy [11, 13], in this study we took a different approach. We designed multicenter, open-label, observational study to assess the impact of early vs. late referral on the effectiveness of renal anemia treatment with ESA in 3 groups of HD patients (treated with ESA less than 3 months before HD, treated with ESA more than 3 months before HD and not treated with ESA before HD) as well as whether treatment with ESA in HD patients can influence the number of cardiovascular events, deaths and hospitalization for CV and other events in Central and Eastern European (CEE) countries. We formulated the following hypotheses: group A (not treated with ESA) patients will have more profound anemia at baseline than patients in group B (treated with ESA less than 3 months before HD), and group B patients will have more profound anemia than patients from group C (treated with ESA more than 3 months before HD); the baseline differences in anemia parameters will decrease with the time of the study, and

at the end of the study no differences between the groups will be observed (end of study anemia A = end of study anemia B = end of study anemia C); early referral to ESA therapy decreases the number of cardiovascular events (CV events group A > CV events group B > CV events group C). We also looked at the kidney function at the time of diagnosis of CKD and the start of ESA therapy, including the new CKD-EPI formula. Herein, we present the baseline data of the studied groups.

Patients and Methods

Patients suitable for the study had to fulfill the following inclusion criteria: stable hemodialyzed patients with renal anemia who were no longer than 12 months on HD and who were on ESA therapy; no fluctuation of Hb more than 2 g/dl/month within the last 3 months of ESA treatment; adult (age ≥ 18 years); signed informed consent. 50 centers in 3 countries participated in the study. 398 hemodialyzed patients (231 males, 167 females) aged 19–90 years (57.5 ± 14.7) on standard ESA therapy for chronic renal anemia were recruited. The following retrospective and prospective parameters had been collected during the study and were analyzed. Retrospective parameters: the date of CKD diagnosis (Hb concentration, iron concentration; source of referral to nephrologists; the date of start of predialysis care (Hb concentration, iron concentration, serum creatinine and eGFR calculated according to Cockcroft-Gault [14], Modification of Diet in Renal Disease (MDRD) [15] and CKD-EPI formulae [16]); period of renal anemia treatment; date of start of HD; all major CV events in patient's history (MI, PCI, coronary artery bypass grafting, stroke, TIA). The data were collected in electronic Data Capture system. Data were verified for logical and medical consistency according to the instructions provided in CTAP. In the case of inconsistencies, data query was generated and was sent for investigator's review. A part of problems was resolved; however, some queries were not addressed by investigators. Unresolved issues were related to missing data allowing to allocate patient to specific study group (15 patients), discrepancies between laboratory results and acceptable range of results, and AE description. All available and logically acceptable data were analyzed.

Patients were divided into three groups: group A – patients not treated with ESA before start of dialysis; group B – patients who had started ESA therapy within 3 months from start of dialysis; group C – patients who had started the ESA therapy more than 3 months before start of dialysis.

Comparisons were performed for all patients allocated to one of the groups. Patients without allocation were excluded from analysis.

Statistical Analysis

The data recorded in the database were provided for analysis in the Excel format.

The data were analyzed using SAS statistical software. The χ^2 test was used for analysis of qualitative data and the Kruskal-Wallis test for quantitative data. p value ≤ 0.05 was defined as statistically significant.

Fig. 1. Patient status at 12 months of the study.

Fig. 2. Distribution of the diagnosis leading to renal failure.

Results

Baseline Patient Characteristics

Fifty centers participated in the study. The number of patients recruited at a single center varied from 1 to 23 (mean 8 ± 5). The highest number of patients (267) was recruited in 30 centers in Poland (mean number of patients per center 9 ± 5). 12 centers in Latvia recruited 81 patients (7 ± 5) and 8 centers in Serbia recruited 50 patients (6 ± 3). 269 patients completed 12 months of therapy. The reasons for study discontinuation are provided in figure 1.

Based on the start dates of ESA and dialysis therapy, patients were allocated to groups A, B and C. Group A: 180 subjects (106 males, 74 females) aged 19–86 years

(56.2 ± 14.4 years); group B: 164 subjects (94 males, 70 females) aged 19–90 years (57.6 ± 14.9 years); group C: 39 subjects (21 males, 18 females) aged 20–86 years (61.8 ± 16 years).

No statistically significant differences between groups A, B and C in age and sex distributions were found. 15 patients could not be classified into any of the groups and were excluded from comparative analysis. Groups A, B and C did not differ in baseline values of arterial blood pressure, body weight or height and BMI.

Causes of CKD

The reasons for CKD were equally distributed (fig. 2).

The diagnosis of CKD was established at the age between 6.5 and 86.3 years (53.6 ± 15.7). No statistically

Fig. 3. Duration of CKD in patients from groups A, B and C.

significant differences in the age at CKD onset were noted between groups A, B and C. CKD was ongoing for the period from few days to 41 years before study start (4.2 ± 5.6). The duration of CKD in group C patients was significantly longer than in groups B and A (fig. 3).

Medical History and Concomitant Diseases

The protocol predefined the categories of concomitant diseases of special interest (fig. 4). Compared with groups A and C, group B had a significantly lower rate of patients with left ventricular hypertrophy (53 and 64 vs. 39%, respectively, $p = 0.004$) and secondary hyperparathyroidism (43 and 44 vs. 25%, $p = 0.001$). The frequency of remaining concomitant diseases did not differ between groups A, B and C.

Forty (10%) patients had a history of myocardial infarct. Other serious heart episodes were less frequent (fig. 5). The rate of patients with the history of heart disease did not differ between groups A, B and C.

Retrospective Data on CKD Diagnosis

At the CKD diagnosis, the mean hemoglobin concentration in all patients was below lower reference limit (10.3 ± 2.3 g/dl); however, the ferritin concentration (222 ± 182 μ g/dl), serum iron concentration (10.4 ± 5.5 μ mol/l) and transferrin saturation ($28 \pm 18\%$) were within reference limits (table 1). No differences in these parameters were observed between groups A, B and C. Patient weight at the onset of the disease varied from 24 to 130 kg (mean 74 ± 17 kg), and the body weight at the onset of renal failure was comparable in all groups. Mean creatinine concentration at the disease diagnosis was 4.7 ± 3.6 mg/dl. GFR according to the MDRD formula was 21.8 ± 17.9 ml/min and creatinine clearance according to Cockcroft-Gault formula

Table 1. Baseline patient characteristics in the 3 groups

	Total (n = 398)	Group			p
		A (n = 186)	B (n = 165)	C (n = 38)	
Sex					0.9266
Male	231	109	95	21	
Female	167	77	70	17	
Age					0.0648
Mean	57.49	56.42	57.60	62.05	
SD	14.71	14.33	14.89	16.48	
Median	58.00	58.00	58.00	66.50	
Height					0.8144
Mean	168.62	168.93	168.04	169.42	
SD	9.89	9.65	10.16	10.50	
Median	168.00	169.00	169.00	167.00	
Systolic BP					0.6756
Mean	138.19	138.53	138.28	135.92	
SD	20.63	21.28	20.79	18.34	
Median	140.00	140.00	139.00	137.50	
Diastolic BP					0.1629
Mean	79.63	79.22	80.70	77.47	
SD	11.46	11.99	11.49	9.17	
Median	80.00	80.00	80.00	80.00	
Weight					0.1390
Mean	73.08	73.30	71.88	76.66	
SD	15.57	15.10	16.23	16.23	
Median	71.00	72.00	70.00	75.00	
BMI					0.1729
Mean	25.67	25.67	25.42	26.65	
SD	4.96	4.92	5.14	4.75	
Median	24.64	25.12	24.17	25.81	

la 24.6 ± 205 ml/min. Group C patients had slightly lower creatinine concentration and significantly higher GFR/creatinine clearance calculated by MDRD or Cockcroft-Gault formula than patients from groups A and B. The diagnosis of CKD was established by nephrologist in 142 (35.7%) and by internist in 141 (35.4%) patients. Causes of CKD and concomitant disease in the 3 studied groups are given in the tables 2 and 3, respectively.

Retrospective Data on Predialysis Care

No statistically significant differences in hematology parameters, creatinine concentration or creatinine clearance between groups A, B and C were observed in the predialysis period.

Retrospective Data on HD Start

HD therapy in the whole group started at the mean age of 57.4 ± 14.9 years. No differences in mean age at HD start were observed between groups A, B and C. The

Fig. 4. Number of patients with presence of predefined concomitant disease.

Fig. 5. Frequency of cardiovascular episodes in patient history.

Table 2. Causes of CKD in the 3 studied groups

	Total (n = 398)	Group			p
		A (n = 186)	B (n = 165)	C (n = 38)	
Diabetic nephropathy	75 (18.84)	30 (16.13)	36 (21.82)	8 (21.05)	0.6795
Glomerulonephritis	64 (16.08)	30 (16.13)	23 (13.94)	9 (23.68)	
Hypertensive nephrosclerosis	61 (15.33)	35 (18.82)	22 (13.33)	3 (7.89)	
Pyelonephritis/interstitial nephritis	79 (19.85)	36 (19.35)	31 (18.79)	9 (23.68)	
Polycystic kidney disease	38 (9.55)	18 (9.68)	17 (10.30)	2 (5.26)	
Not known	48 (12.06)	24 (12.90)	19 (11.52)	4 (10.53)	
Other	33 (8.29)	13 (6.99)	17 (10.30)	3 (7.89)	

Figures in parentheses indicate percentages.

Fig. 6. Duration of HD in patients from groups A, B and C.

Fig. 7. Duration of prestudy ESA therapy.

Table 3. Concomitant diseases in the 3 studied groups

	Total (n = 398)	Group			p
		A (n = 186)	B (n = 165)	C (n = 38)	
Diabetes	102 (25.63)	42 (22.58)	48 (29.09)	11 (28.95)	0.3460
Hypertension	354 (88.94)	162 (87.1)	147 (89.09)	37 (97.37)	0.1834
Coronary heart disease	113 (28.39)	53 (28.49)	42 (25.45)	15 (39.47)	0.2230
Chronic heart failure	115 (28.89)	52 (27.96)	43 (26.06)	17 (44.74)	0.0680
Left ventricular hypertrophy	192 (48.24)	98 (52.69)	65 (39.39)	24 (63.16)	0.0066
Peripheral occlusive disease	50 (12.56)	26 (13.98)	17 (10.3)	7 (18.42)	0.3296
Dyslipidemia	171	89	64	18	0.2109

Figures in parentheses indicate percentages.

mean duration of the dialysis treatment in the whole group was 180 ± 105 days. Patients from group A were longer on dialysis therapy than patients from groups B and C (fig. 6).

The mean value of hemoglobin concentration in the whole group was below lower reference limit (9.26 ± 1.7 mg/dl). Mean serum iron concentration (10.2 ± 5.78 μ mol/l), and transferrin saturation ($23.65 \pm 16.4\%$) were close to the lower reference limit value. No statistically significant differences in hematology parameters were observed between groups A, B and C.

Retrospective Data on ESA Therapy Start

Mean duration of prestudy ESA therapy in the whole group was 207 ± 203 days. Patients from group C received ESA for statistically significantly longer than those from groups A and B (fig. 7).

As per protocol, none of patients from group A received ESA before HD. ESA in this group started at a

mean of 39 ± 17 days after start of HD. Patients from group B received ESA within 90 days before dialysis (5 ± 14 days), and those from group C had received ESA more than 90 days before start of HD (423 ± 426 days).

The most frequently used ESA formulation was Epo beta – NeoRecormon (70%). Epo alpha was used in 16% and darbepoetin alpha in 14% of patients. The subcutaneous route of administration was used in 62% and the intravenous route in 38% of patients. The rate of patients receiving ESA subcutaneously in group C (92%) was significantly higher than in groups A and B. The mean weekly dose of ESA in all patients was $5,621 \pm 3,271$ units. Mean prestudy weekly dose of ESA in group C was statistically lower than in group A and B patients ($3,823 \pm 3,168$ vs. $5,275 \pm 2,915$ and $6,426 \pm 3,441$ units/week, respectively, $p < 0.001$).

At the start of ESA therapy, mean hemoglobin concentration was 9.24 ± 1.42 g/dl, ferritin 245.6 ± 245.8 mg/dl, serum iron 11.29 ± 6.25 μ mol/l and transferrin satu-

Table 4. Summary data at prestudy ESA start

GFR/ creatinine clearance, ml/min	Total (n = 398)	Group			P
		A (n = 180)	B (n = 164)	C (n = 39)	
MDRD					<0.001
n	285	133	119	33	
Min	2.36	2.36	2.60	8.42	
Max	44.08	36.28	44.08	25.31	
Mean	9.39	8.03	9.21	15.57	
SD	5.08	4.28	4.50	5.59	
Median	8.36	6.84	8.78	14.74	<0.001
Cockcroft-Gault					
n	269	125	114	30	
Min	3.34	3.34	3.95	11.28	
Max	67.69	48.70	67.69	38.11	
Mean	12.87	11.36	12.57	20.31	
SD	6.70	5.32	6.79	6.85	<0.001
Median	11.66	10.19	11.72	18.97	
CKD-EPI					
n	235	113	95	27	
Min	1.97	1.97	2.33	7.7	
Max	35.66	35.66	15.99	23.81	
Mean	8.52	7.52	7.97	14.72	
SD	4.53	4.28	3.05	5.18	
Median	7.56	6.43	7.73	14.57	

ration $24.5 \pm 12.8\%$. No statistically significant differences were observed between groups A, B and C. Body weight at the beginning of ESA therapy did not differ between the groups.

Mean serum creatinine at the start of ESA therapy was 7.2 ± 2.86 mg/dl. Mean creatinine clearance according to MDRD formula was 9.4 ± 5.8 ml/min, according to Cockcroft-Gault formula 12.87 ± 6.7 ml/min and according CKD-EPI formula 8.52 ± 4.53 ml/min. The differences in creatinine concentration and clearance were statistically significant (table 4).

No differences in adverse events profile including serious adverse events, drug-related adverse events or cardiovascular events were observed between groups A, B and C in our study.

Discussion

We demonstrated for the first time that in CEE countries the majority of patients with CKD receive ESA therapy shortly before or after start of dialysis treatment. The US Renal Data System Assessment study retrospectively

examined hematocrit and erythropoietin use in CKD patients using Medicare data collected from across US states between 1994 and 2000 [17]. The study identified a close correlation between the extent of erythropoietin use and hematocrit, and found that both hematocrit values increased significantly after release of the US NKF-DOQI guidelines [18, 19]. These findings suggested that, in the US, the guidelines might have had a favorable impact on outcomes in renal anemia. In contrast, a number of observational studies have indicated substantial deficiencies in the management of renal anemia in EU countries [13, 20, 21]. Therefore, we addressed the similar question of renal anemia treatment in large Eastern and Central European countries. The European Survey on Anaemia Management (ESAM) prospectively examined 14,527 CKD patients referred for dialysis across 14 countries, including Poland and Slovenia [13]. The Predialysis Survey on Anaemia Management (PRESAM) study is a retrospective observational study that included 4,333 patients, who commenced dialysis between September and November 1999 [20]. These surveys found that >5% of patients had Hb <11 g/dl and 80% of patients had Hb <10 g/dl when erythropoietin treatment was commenced, considerably lower than the NKF [19, 20] and EBPG recommendations [22]. Furthermore, fewer than 20% of patients had achieved target Hb when dialysis was instituted [20]. The ESAM study found that as few as 11 and 31% of patients had received erythropoietin before HD and CAPD, respectively [13]. These data suggest that clinicians may be underestimating the importance of identifying and adequately treating renal anemia, or that there is a lack of awareness of the EBPG recommendations for optimal treatment and target Hb concentrations. In the Dialysis Outcomes and Practice Patterns Study (DOPPS) [23], a prospective, observational study based on data collected from nationally representative samples of HD facilities that examine anemia management and outcomes, European countries included in the DOPPS were France, Germany, Italy, Spain and the UK (EuroDOPPS) [24]. In 2000, 84% of prevalent HD patients were prescribed ESA. In our study, performed much later, early ESA therapy (more than 3 months before HD) was reported in approximately 10% of patients only [24]. This is in huge contrast to the ORAMA study [11], where almost all nondialysis patients (98%) received ESA therapy during the prestudy period and at baseline, primarily s.c. epoetin beta (95%). In comparison, in PRESAM, only 26% of patients were reported to have started ESA treatment before dialysis [20]. The decision about early introduction of ESA did not depend on the reason for CKD, patient's age or sex; how-

ever, it seemed that patients who received early ESA therapy suffered longer from CKD than those who received ESA later. It appears that this phenomenon is related to the tight reimbursement policy. In general, we can only compare our data with the ORAMA study, where separate results for Eastern Europe were provided. In the prestudy period, patients treated early with ESA required lower doses of ESA than those who received ESA therapy shortly before or just after starting dialysis. This also appears to be related to the reimbursement policy in these countries. We also demonstrated for the first time that the diagnosis of CKD in the majority of patients (71%) in CEE countries was established by the nephrologist or internist. In general, the diagnosis of CKD was made when patients had at least stage 3 CKD, in the majority of cases stage 4. At the time of diagnosis, most patients had anemia. We calculated eGFR using three different formulae, including the novel CKD-EPI formula. In our study with patients with at least stage 3 CKD, eGFR using CKD-EPI was similar to MDRD; however, with the tendency to lower values particularly in group C (with the longest history of CKD, who started ESA at least 3 months before HD). In general, on the basis of the reported eGFR at the time of diagnosis of CKD, it seems that there is still huge room for improvement of early detection of CKD and nephrological care. Results by Rayner et al. [25] from the DOPPS have shown that 81% of EuroDOPPS patients saw a nephrologist at least 1 month prior to starting dialysis (country range 72–87%), and 76% saw a nephrologist more than 4 months prior to starting dialysis [24]. In PRESAM study, the majority of CKD patients had been under specific nephrologist control, but only 27% received ESA [21].

During the predialysis care, hematological parameters (hemoglobin, ferritin, serum iron concentration and transferrin saturation) remain stable. At start of dialysis mean hemoglobin value was lower than at the beginning of the disease (9.26 ± 1.7 vs. 10.3 ± 2.3 g/dl, respectively). At the beginning of ESA therapy, the mean hemoglobin value was 9.24 ± 1.4 g/dl, similar to the low mean hemoglobin concentration of 9.4 g/dl displayed by new ESRD patients when initiating HD in EuroDOPPS in 1998–2000. This underscores the failure of pre-ESRD health care programs to adequately address the anemia management needs in this patient population. However, in the ORAMA study, 3 out of 5 nondialysis patients had mean prestudy Hb values above the EBPG target of 11 g/dl, which is a higher rate than among dialysis patients [11]. Patients who entered the study had already been treated with ESA, and mean hemoglobin at the baseline

visit was higher than at ESA start (11.04 ± 1.38 g/dl). During all subsequent study visits, mean hemoglobin value in the whole study group was stable and varied from 11.04 to 11.26 g/dl. It was consistent with the new European Best Practice Guidelines [26], which were the first to address this issue in the post-TREAT era [8]. Now, it is strongly recommended that, for diabetic CKD patients or CKD patients with comorbidities, a new treatment target of 10–12 g/dl (and not the historical target of 11–12 g/dl) is warranted. Group A patients entered the study with lower hemoglobin concentration than the remaining groups, as expected. In this respect, it is difficult to compare our data with the ORAMA study [11], because we look at the incident HD patients and their retrospective data, whereas in the ORAMA trial prevalent HD or CKD patients were randomized to either standard clinical care or computerized clinical decision support [11]. Nevertheless, the mean hemoglobin in Eastern Europe was 10.6 g/dl compared with 11.8 g/dl in Western Europe in the HD population in the ORAMA trial [11].

In general, patients with increased residual renal function as in group C may also demonstrate more endogenous erythropoietin production and therefore a lesser need for ESA therapy. However, no statistically significant differences were observed between groups A, B and C with regard to hemoglobin, ferritin and serum iron. The differences in ESA dose might be attributed to the better residual renal function in group C, less pronounced subclinical inflammation due to better kidney function, better nephrological care (center effect?), or slightly, although not significantly better iron supplementation.

The majority of patients received iron supplementation (86%) and folic acid therapy (68%). No differences between groups A, B and C were noted. In the EuroDOPPS, the fraction of HD patients who were prescribed i.v. iron within a 4-month data collection interval in the year 2000 ranged from 43% of patients in Italy to 71% in Germany [24]. In the ORAMA trial, 64% of the population studied received iron therapy in Eastern Europe, similar to 66% in Western Europe [11]. In the CKD population, Eastern Europe was represented only by Bulgaria, where iron supplementation was given to 60% of the studied patients, while only in 37% in Western Europe. In the GAIN trial, all countries had 46–74% of patients on iron therapy with the exception of Greece (25.6%) and Turkey (23.2%); however, the detailed data are unavailable [12]. No data on iron therapy are available in the ESAM study. The authors provided only data on

iron status (adequate, functional or absolute iron deficiency) in the population studied without detailed results for specific countries [13]. In our study, 31% of patients received blood transfusion, and it was shown that patients who did not receive ESA before dialysis required more transfusions and received more blood than those who had been treated with ESA before dialysis. There are no data provided by ORAMA trial investigators [11, 27], ESAM [13] or GAIN [12].

In conclusion, in CEE countries renal anemia therapy with ESA is started shortly before or after start of HD. The subcutaneous administration route of NeoRecor-mon was most frequently used in standard practice during the period of the study. Prestudy and baseline data reported in our study highlight important differences in standard care in Eastern Europe. However, paradoxically, due to tight reimbursement policy we foresee the clinical implications of the TREAT trial for the CKD population.

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