http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i7.60

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Trends for Response to Erythropoietin Stimulating Agents

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Abstract
There are many causes leading to renal anemia in patients with chronic kidney disease (CKD). There are many factors that contribute to the aggravation of anemia and non-achievement of optimal, targeted hemoglobin levels. The question has been repeatedly discussed, "At what hemoglobin levels should anemia be treated in patients with CKD?" It is also unclear whether patients treated with Erythropoietin Stimulating Agents (ESAs) before hemodialysis, after initiating renal replacement therapy have different hemoglobin levels than ESA-naïve patients prior to dialysis.
Objective of the Follow-Up: *To characterize the trend for response to ESAs in patients who received ESAs before the start of dialysis treatment, compared to patients who were ESA-naïve before starting dialysis treatment.*
Material and Methods: *Over a period of 12 years, the following categories were monitored by sex: age, hemoglobin levels, ESAs dosage in patients on periodic dialysis treatment between 2009 and 2020- 286 female and 489 male patients. The following methods were used: Questionnaire; Hemoglobin test; Statistical methods – methods of prospective follow-up, Microsoft Office Excel Professional Plus2013 Data analysis – t-Test: Two-Sample Assuming Unequal Variances.*
Results: *1.A very large number of patients have initiated periodic hemodialysis treatment in emergency, without knowing about their disease and were not monitored by a nephrologist and were not treated with ESAs before dialysis.2.There is a statistically significant difference in the mean hemoglobin level in women who were ESA treatment-naïve before HD compared to men who were ESA treatment-naïve before HD (p=0.047006), also ESA dose/kg body weight (p=0.011646).*
Keywords: *chronic kidney disease (CKD), hemodialysis, anemia, Erythropoietin Stimulating Agents (ESAs).*

Introduction

There are many causes leading to renal anemia in patients with CKD. There are many factors that contribute to the aggravation of anemia and non-achievement of optimal, targeted hemoglobin levels. The question has been repeatedly asked, "At what hemoglobin levels should anemia be treated in patients with CKD?"[1,2]. The answer to the question whether ESA-treated patients before hemodialysis, after initiating renal replacement therapy have different hemoglobin levels and then ESA-naïve patients who have initiated dialysis treatment, remains unclear. In 2010, 2,618,000 patients were treated with hemodialysis worldwide; however, the actual number of patients requiring this type of therapy ranges between 4,900,000 in the conservative model to 9,700,000 in the high-score model. The lack of

access to treatment in less developed countries (some of them in Asia and Africa) means that more than 2,000,000 people do not receive any treatment. It is also estimated that the number of patients on dialysis will increase by approximately 5,000,000 by 2030[3]. Meanwhile, it is estimated that the number of patients with end-stage renal disease will increase by about 6% per year. Nearly 90% of the patients treated with renal replacement therapy undergo extracorporeal blood purification (hemodialysis, hemodiafiltration or their variants) and only about 10–11% undergo peritoneal dialysis[4].

The number of dialysis patients in Bulgaria in the recent years is constantly growing by 3-3.5% and currently exceeds 3,600 people (3,763 in 2017). The European trend shows an increase by 6-7%. However, the number of patients with CKD monitored by a nephrologist, who have been diagnosed and are in the early stages of CKD, and are being monitored, remains small. The development in these patients is clear, but they are a small group: 35% – 40%[5],[6]. Very few patients initiate scheduled periodic hemodialysis treatment with a pre-built and "mature", ready-to-use A-V fistula, and very few patients have received ESAs during the pre-dialysis period. In addition, not all patients who were monitored by a nephrologist arrived for dialysis with a pre-built and "mature", ready-to-use AV fistula, or had manifestation of anemia and received ESAs. These were mostly patients who did not show up on a quarterly basis and were not clinically and paraclinically followed by a nephrologist. The need for detailed studies related to the follow-up of this patient population is at the heart of this paper.

Objective

To characterize the trend to respond to ESAs in patients who received ESAs before dialysis treatment, compared to patients who were ESAs treatment-naïve before starting dialysis treatment.

Material and Methods

Over a period of 12 years, the following categories were monitored by sex: age, hemoglobin levels, ESAs dosage in patients on periodic dialysis treatment in the Department of Dialysis Treatment /DDT/, UMHAT Sveta Anna AD Sofia, between 2009 and 2020. Patients were grouped into two groups: group A – patients who received ESAs before the start of dialysis treatment, and group B – ESA treatment-naïve before starting dialysis treatment. 286 female and 489 male patients were followed. A total of 775 patients. A comparative analysis was performed between group A and group B by sex. The female patients in group A were compared to male patients in group A, and female patients in group B were compared to male patients in group B. The following categories were compared: age, mean hemoglobin level, ESAs mean weekly dose, ESAs mean weekly dose/kg body weight.

Methods: 1. Questionnaire. All study subjects were interviewed using a standardized questionnaire to provide the following data: gender, age, weight, monitoring during the pre-dialysis period, ESAs administration during the pre-dialysis period. **2. Method of hemoglobin testing** (Colorimetric method at the UMHAT "St. Anna" AD Sofia laboratory) **3. Statistical methods.** Statistical Analysis Data was collected and compiled using Microsoft Excel Office Professional Plus 2013 Data analysis – t-Test: Two-Sample Assuming Unequal Variances, The methods of prospective follow-up were used, Descriptive and deductive statistics, Parametric analysis, Descriptive statistics: point estimates of parameters-finding averages.

Results and Discussion

Table 1 and Chart 1 show data of patients who were monitored by a nephrologist before initiating HD; ESAs treatment before HD. Annually, at the beginning of January, patients were interviewed through a standardized questionnaire to provide the following data: gender, age, monitoring during the pre-dialysis period, ESAs administration

during the pre-dialysis period. Patients are examined for complete blood counts and chemistry, the weekly dose per patient is monitored, as well as the weekly dose per kg/weight.

Table 1 presents the data from the follow-up of patients in the years 2009-2020. It is important to note that the patients on periodic hemodialysis treatment who had started such treatment in emergency and patients with previously unknown CKD form much larger proportion.

Chart 1and Chart 2 presents the data from Table 1.Chart 2 presents the data from Table 1in relative-percentage.

It is obvious at first glance that there is a large number of patients who initiated emergency treatment. In all those 12 years, the percentage of monitored patients before the initiation of periodic hemodialysis treatment was not higher than 53.62%. The highest number of patients was observed in 2014 – 53.62%, and the lowest number of patients was observed in 2018 – 25.4%. The statistics are similar for patients who received ESAs during the pre-dialysis period. The highest is the number of monitored patients who received ESAs in 2010 – 34.78%, and the lowest in 2018 – 15.78%. The data for the USA for the period 1995-2012 were similar[7] +. While in the USA this rate was around 15% by 2012, the rate at DDT, Sveta Anna Hospital AD Sofia was between 15.78% and 34.48% for the period 2009-2020.

Women who initiated HD and had previously received ESAs had a mean age of 61.533±1.9 years. Women who initiated dialysis without using ESAs were at the average age of 58.09±0.997. The largest number (9) with a relative share of 47.36% of all women receiving ESA before HD in 2010. In general, the total number of female patients in the dialysis facility during the follow-up years was always about twice less than the male patients on dialysis. These data correspond to data from otherdialysis structures in Bulgaria, as well as to data published worldwide, i.e. that female patients have a significantly smaller share among dialysis patients compared to male patiens[8] ,[9] .

Table 2 shows patient monitoring by age structure.

There is no statistically significant difference in the age of female patients who received ESAs before HD (group A) and those who initiated HD without receiving ESAs treatment (group B) (p=0.129). In male patients, there is also no statistically significant difference between the two groups (p=0.1019). In addition, there is no statistically significant difference in the age of women compared to men receiving ESAs (group A) (p=0.81). There is no statistically significant difference in the age of women compared to men who were ESA treatment-naïve (p=0.4017) (group B).

Mean hemoglobin levels, ESAs average weekly dose, ESAs average weekly dose per kg/weight in both groups (compared by sex) were examined during the follow-up. The results are presented in Tables 3,4,5.

Comparing the data from the results, it was found that there is no statistically significant difference in the mean hemoglobin levels of the two groups of female patients (group A compared to group B, i.e. patients who received ESAs or were ESAs treatment-naïve before the start of HD) (p=0.1373). No such difference was found in men (p=0.246). The results for the period 1995-2012 are similar for patients from the USA in terms of hemoglobin levels and comparison of the two groups of patients, i.e. with and without ESAs treatment. There is no gender grouping in their follow-up[1°]. However, in our patients, there was a statistically significant difference in the mean hemoglobin level of female patients who were ESAs treatment-naïve (group B) before HD compared to male patients (group B) who were ESA treatment-naïve (p=0.047006). Female patients showed significantly lower hemoglobin level (9.345±0.25 g/l). In male patients, the mean value was 9.95±0.13 g/l. When comparing the mean hemoglobin levels in men and women

receiving ESAs (group A) there is no significant difference (p=0.833).

There is no data in the world literature to compare the results of the two groups of patients (with ESAs treatment; ESAs treatment-naïve before HD) in relation to ESA mean weekly dose, ESAs mean weekly dose per kg/body weight, or ERI.

The following Table 4 presents the data for the two female patient groups by ESAs mean weekly dose and ESA mean weekly dose per kg/body weight. Table 5 shows the same indicators for men. There is no statistically significant difference between the two female patient groups (group A) compared to group B in terms of mean weekly dose (p=0.704) and mean weekly dose per kg/weight (p=0.827).

During the calculations, the following results were obtained according to the ESA mean weekly dose indicator:

Female patients group A / Female patients group B, p=0.739

Male patients group A / Male patients group B, p=0.2568

Female patients group A / Male patients A, p = 0.2870

Female patients group B / Male patients group B, p = 0.18986 According to this indicator there is no statistical difference between groups A and B, nor a difference by sex.

According to indicator ESA mean weekly dose/kg, the results are as follows:

Female patients group A / Female patients group B, p=0.85

Male patients group A / Male patients group B, p=0.870

Female patients group A / Male patients group A, p=0.399

Female patients group B / Male patients group B, p=0,0116

There was a statistically significant difference in ESA mean dose/kg body weight in women who were ESA treatment-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.0116). Female patients show significantly higher mean dose – mean value (134.58±6.835 E/kg). For men, the mean value is 109.18±6.2061 E/kg.

The result of the long-term 12-year follow-up of the patients in the Department of Dialysis Treatment, Sveta Anna Hospital AD Sofia shows:

1. A very large number of patients have initiated periodic hemodialysis treatment in emergency, without knowing about their disease and were not monitored by a nephrologist.
2. There is a high percentage of patients on periodic hemodialysis treatment who were not treated with ESAs before dialysis.
3. There is a statistically significant difference in the mean hemoglobin level in women who were ESA treatment-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.047006). Female patients show a significantly lower hemoglobin level: 9.345±0.25 g/l. In male patients, the mean hemoglobin value is 9.95±0.13 g/l.
4. There is a statistically significant difference in the mean ESA dose/kg body weight in women who were ESA-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.0116). Female patients show a significantly higher mean dose – mean value: 134.58±6.835 E/kg. In male patients, the mean value is 109.18±6.2061E/kg.
5. There is no difference in the age of the two groups of patients compared by sex and between the sexes, or in ESA mean weekly dose.
6. There is no statistically significant difference between the sexes when comparing ESA mean weekly dose/kg weight in group A (those who received ESA treatment before HD), p=0.399.
7. No similar results have been published in the medical literature.

Table 1. The data from the follow-up of patients in the years 2009-2020

Year	2009N(%)	2010N(%)	2011N(%)	2012N(%)	2013N(%)	2014N(%)	2015N(%)	2016N(%)	2017N(%)	2018N(%)	2019N(%)	2020N(%)
Monitored by nephrologist before HD	23 (29,49%)	24 (52,17%)	22 (40%)	24 (35,29%)	32 (43,24%)	37 (53,62%)	24 (37,5%)	24 (31,58%)	20 (32,79%)	16 (25,4%)	21 (30,88%)	15 (29%)
Received ESA treatment before HD	17 29,49(%)	16 (34,78%)	12 (21,82%)	17 (25%)	21 (38,38%)	12 (17,39%)	17 (26,56%)	21 (27,63%)	15 (24,57%)	10 (15,87%)	12 (17,67%)	10 (17,67%)
Total patients on HD with ESA	78	46	55	68	74	69	64	76	61	63	68	53

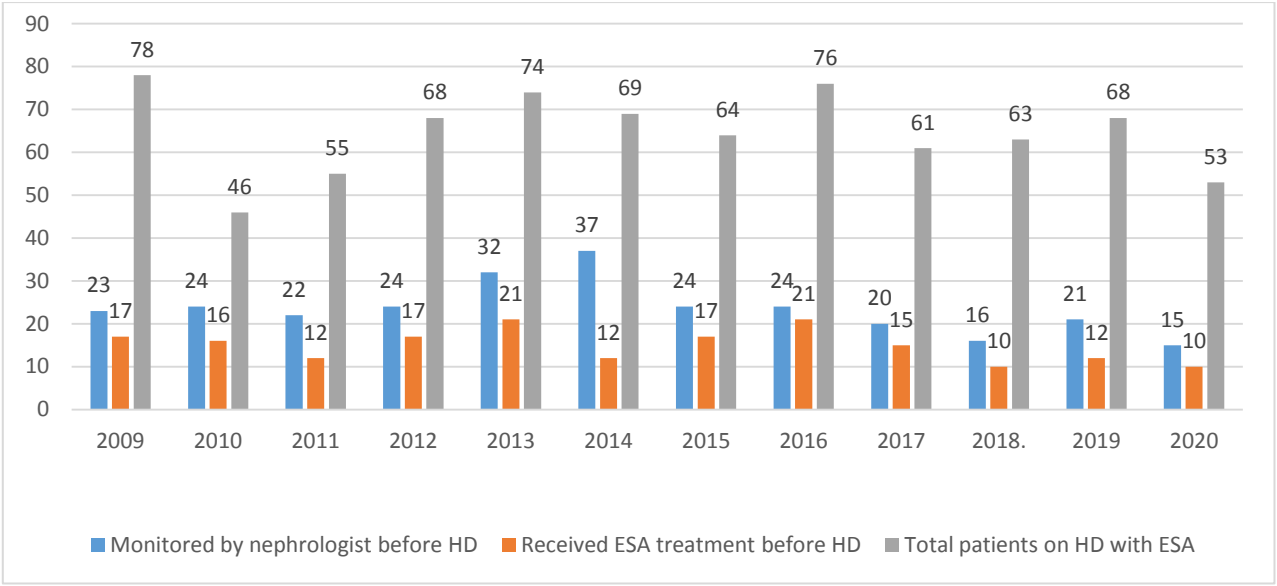

Chart 1. The data from the follow-up of patients in the years 2009-2020

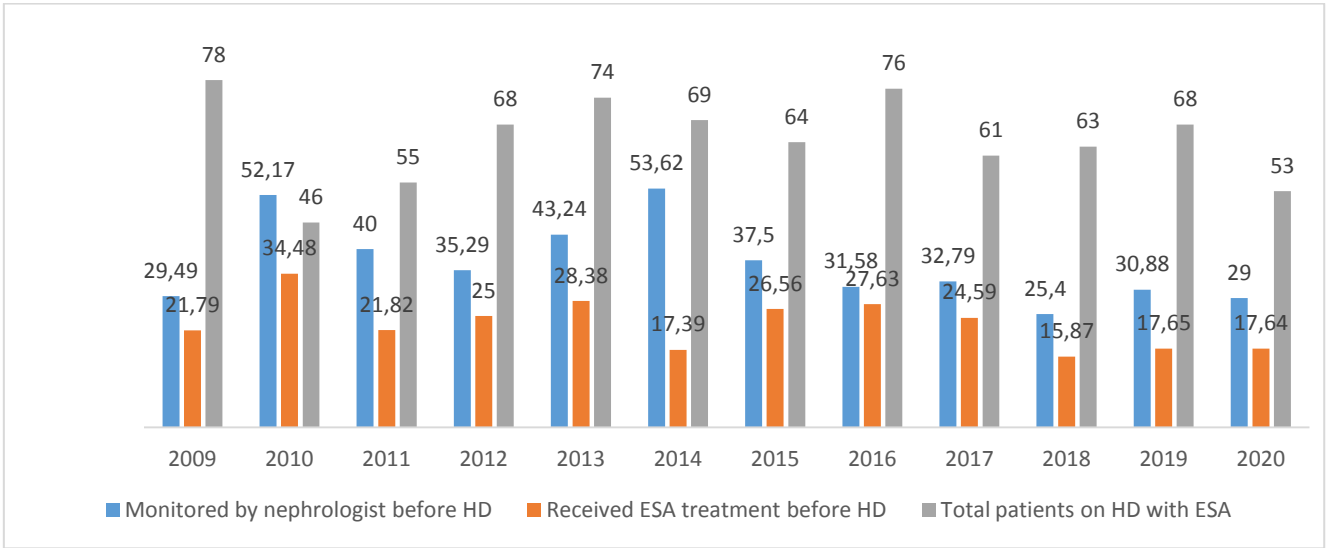

Chart 2. The data from the follow-up of patients in the years 2009-2020in relative percentage

Table 2. Age structure

Year	Total number female patients	Female patients receiving ESA before HD (group A) N (%)	Mean age of female patients receiving ESA before HD (group A)	Mean age of ESA treatment-naïve female patients before HD (group B)	Total number male patients	Male patients receiving ESA before HD (group A) N (%)	Mean age of female patients receiving ESA before HD (group A)	Mean age of ESA treatment-naïve male patients before HD (group B)
2009	30	9 (30%)	53.78±5.4 min.-36; max.-84	61.28±3.9 min.-19; max.-83	48	8 (17%)	55.87±6.34 min.-35 max.-83	58±2.31 min.-21 max.-83
2010	19	9 (47.36%)	53.88±5.44 min.-36; max.-84	57,9 ± 5,6 min.-19; max.-76	27	7 (20.58%)	58.57±6.63 min.-35 max.-83	55.07±2.98 min.-21 max.-80
2011	22	7 (31.8%)	54.14±5.96 min.-35; max.-77	58.93±7.67 min.19; max.- 82	33	5 (15.15%)	56.2±6.53 min.-35 max.-74	60.82±2.82 min.-21 max.-81
2012	19	7 ((31.84%)	52.57±6.097 min.-37; max.-78	51.33±6.06 min.-20; max.-77	49	10 (20.48%)	58.8±4.471 min.-36 max.-77	57.51±2.3 min.-22 max.-83
2013	30	12 (40%)	60.16±4.456 min.-38; max.-78	58.88±4.48 min.-21; max.-79	44	8 (18.18%)	59±5.56 min.-37 max.-78	56.91±2.34 min.-23 max.-84
2014	27	5(18.51%)	63.66±2.08 min.-56; max.-71	56.72±3.84 min.-22; max.-80	42	7(16.66%)	65.14±5.5 min.-43 max.-84	60.51±2.4 min.-24 max.-83
2015	24	7(29.16%)	65.28±2.02 min.-57; max.-72	56.64±4.48 min.-23; max.-81	40	10(25%)	67.2±4.439 min.-44 max.-85	62.46667±2.529 min.-25 max.-84
2016	28	9(21.14%)	60.55±3.21 min.-44; max.-72	53.32±3.65 min.-24; max.-80	48	12(25%)	63.333±2.8159 min.-45 max.-78	58.79±2.34 min.-26 max.-85
2017	27	8(29.62%)	69.25±1.58 min.-62; max.-74	58.,47±2.78 min.-29; max.-72	44	7(15.9%)	59±4.9038 min.-43 max.-79	58.43±2.29 min.-27 max.-72
2018	22	6(27.27%)	70±1.61 min.-66; max.-75	58.62±4.35 min.-62; max.-74	41	4(8.8%)	61.25±2.21 min.-57 max.-66	57.56±2.25 min.-**28** max.-79
2019	19	7(36.84%)	65.85±6.56 min.-32; max.-77	60.5±5.53 min.-31; max.-83	39	6(15.38%)	61.,83±2.833 min.-52 max.-70	60.87±2.7960 min.-29 max.-80
2020	19	5(30%)	69.28±5.7 min.-47; max.-78	64.5±4.398 min.-31; max.-83	34	5(14.7%)	65.8±3.3526 min.-53 max.-72	59.82±2.39 min.-30 max.-79
		Mean	61.53333333	58.09083333		Mean	60.99666667	58.89638917
		Standard Error	1.916790773	0.997319482		Standard Error	1.075775501	0.597510482
		Minimum	52.57	51.33		Minimum	55.87	58.89638917
		Maximum	70	64.5		Maximum	67.2	0.597510482

Table 3. The hemoglobin levels

Year	Total number female patients	Female patients receiving ESA before HD (group A) N (%)	Mean hemoglobin level in female patients receiving ESA before HD (group A)	Mean hemoglobin level in ESA treatment-naïve female patients before HD (group B)	Total number male patients	Male patients receiving ESA before HD (group A) N (%)	Mean hemoglobin level in male patients receiving ESA before HD (group A)	Mean hemoglobin level in ESA treatment-naïve female patients before HD (group B)
2009	30	9(30%)	9.91±0.66 min.-6; max.-12.2	10.39±0.223 min.-8.1; max.-12.4	48	8(17%)	10.61±0.386 min.-8.9 max.-12.4	10.42±0.221 min.-6.7 max.-13.7
2010	19	9(47.36%)	9,8±0,66 min.-6; max.-12.2	10.78±0.387 min.-19; max.-83	27	7(20.58%)	10.71±0.43 min.-8.7 max.-12.4	10.38±0.33 min.-6.7 max.-13.7
2011	22	7(31.8%)	9.81±0.26 min.-8.8; max.-10.8	10.48±0.12 min.-9.8; max.-11.6	33	5(15.15%)	9.28±0.361 min.-8.1 max.-10.1	10.48±0.091 min.-9.7 max.-11.7
2012	19	7(31.84%)	9.82±0.158 min.-9.3; max.-10.4	9.716±0.313 min.-7.8; max.-11.6	49	10(20.48%)	9,86±0,2569 min.-8,1 max.-11,4	10.37±0.12 min.-7.8 max.-11.9

2013	30	12(40%)	9.933±0.3875 min.-8.5 ; max.-13.2	9.7166±0.4339 min.-6.8; max.-13.9	44	8(18.18%)	9.35±0.54 min.-6.3 max.-11.4	10.263±0.2628 min.-6.2 max.-13.7
2014	27	5(18.51%)	9.75±0.5129 min.-8.2 ; max.-11.4	9.0545±0.362 min.-6; max.-133	42	7(16.66%)	9.5±0.5761 min.-6,3 max.-11,2	9.3771±0.2824 min.-5.2 max.-12,2
2015	24	7(29.16%)	10.142±0.4275 min.-8.8; max.-12.4	8.8117±0.4548 min.-5,1; max.-12,1	40	10(25%)	9.36±0.6155 min.-4.9 max.-11.6	9.566±0.2895 min.-6.7 12.6
2016	28	9(21.14%)	9.922±0.4342 min.-7.7; max.-12	9.4842±0.2527 min.-6.9; max.-11.4	48	12(25%)	9.7916±0.3462 min.-8.2 max.-11.7	9.8556±0.3113 min.-5.7 max.-13.5
2017	27	8(29.62%)	9.93±0.486 min.-8.4; max.-11.7	8.3±0.468 min.-6; max.-12.6	44	7(15.9%)	8.857±0.6252 min.-7.1 max.-11.8	9.4918±0.2935 min.-7.1 max.-13.3
2018	22	6(27.27%)	8.62±1.50 min.-7.6; max.-11.2	8.33±0.540 min.-4.4; max.-10.9	41	4(8.8%)	10.55±0.3095 min.-9.7 max.-11.1	9.587805±0.2751 min.-5.7 max.-13.3
2019	19	7(36.84%)	9.78±0.456 min.-8.4; max.-11.3	8.55±0.44 min.-5.2; max.-10.8	39	6(15.38%)	9.3±0.6865 min.-6.8 max.-11.5	10.3±0.28 min.-7.3 max.-14.4
2020	19	5(30%)	9.89±0.517 min.-8.4; max.-11.3	8.64±0.41 min.-4.9; max.-10.4	34	5(14.7%)	9.62±0.3813 min.-8.2 max.-10.3	9.3482±0.3050 min.-6.7 max.-13.8
		Mean	9.731666667	9.345			9.731666667	9.952608333
		Standard Error	0.172674301	0.251424728			0.172674301	0.131463361
		Minimum	8.85	8.3			8.85	9.34
		Maximum	10.71	10.78			10.71	10.48

Table 4. ESAs mean doses in female patients

Year	ESA mean weekly dose (IU) in female patients receiving ESA before HD (group A)	ESA mean weekly dose (IU/kg) in female patients receiving ESA before HD (group A)	ESA mean weekly dose (IU) in female patients who were ESA treatment-naïve before HD (group B)	ESA mean weekly dose (IU/kg) in female patients who were ESA treatment-naïve before HD (group B)	ср. доза ЕСА при мъже, получаващи ЕСА преди ХД	ср. доза ЕСА IU/kg/при мъже, получаващи ЕСА преди ХД на кг/тегло	ср. доза ЕСА IU при мъже, Неполучаващи ЕСА преди ХД	ср. доза ЕСА /IU/kg при мъже, Неполучаващи ЕСА преди ХД
2009	9413.33±2396.759 min.-1000; max.-20200	165.85±46.58 min.17.85; max.-412.6531	9071±13861.27 min.-2000; max.-24000	139.57±18.1994 min.-32.78 315.78	9750±2136,001 min.-2000 max.-19000	126,7959±27,526 min.-17,69912 ; max.-243,5897	7282,051±768,122 min.-0 max.-20000	94,72±9,64 min.-0 max.-225
2010	9191.11±2411.8 min.-1000; max.-20200	162.7701±47.020 min.-17.85; max.-412.65	5050±539.8 min.-2000; max.-8000	82.46248±11.32045 min.-32.7868; max.-150	9428,571±2458,5 min.-2000 max.-19000	122,05±31,30962 min.-17,699 ; max.-243,52	6666,667±1007,451 min.-0 max.-19000	90,1036±15,236 min.-0 max.-330,4348
2011	8428.571±2671.33 min.-0; max.-18000	119.6414±36.9577 min.-0; max.-257.142	6066.667±987.86 min.-2000 max.-15000	94.61874229±14.9943782 min.-28.1690; max.-223.8806	9000±2569,047 min.-2000 max.-18000	132,627916±44,30332765 min.-23,255 ; max.-290,3226	8714,286±866,57,7 min.-2000 max.-18000	112,26252±10,785230 min.-28,571 ; max.-238095
2012	6714.286±808.122 min.-3000; max.-9000	108.1151767039±16.6197 min.-46.87; max.-173.076	8166.667±1471.102 min.-0 max.-18000	127.062293±24.85890 min.-0; max.-260.86956	6700±1085,766 min.-0 max.-12000	90,52945±17,1072 min.-0 max.-193,548387096774	7205,125±556,1331 min.-0 max.-12000	91,70±7,21373 min.-0 max.-184,61538461

		130.56726083±21.59440	9000±983.5244	137.63549±18.46786940	9750±1472,971	127,420376793965±21,83873	7000±768,42	91,0820750±10,39
2013	8500±1322.88	min.-0	min.-0	min.-0	min.-0	min.-0	min.-0	min.-0
	min.-0; max.-12000	max.-230,7692	max.-12000	max.-279.06977	max.-12000	max.-193,55	max.-12000	max.-222,222
		117.2565767±32.29398	10045.45±748.6706	148.682±13.454799	9571,429±1411,806	117,070624696326±18,5228874	8428,571±757,35	107,11796856±9,7691677
2014	9333.333±2458.545	min.0	min.-0	min.-0	min.-2000	min.-23,8095238095238	min.-0	min.-0
	min.-0; max.-16000	max.-210.526315789474	Max.-12000	Max.-226.4150943	max.-12000	max.-176,470588235294	max.-12000	max.-184,6154
		96.99754631776 61±19.876	9411.,765±1141.01	141.62776±16.279586	9400±1857,118	110,97196710561±20,4767680	7333,333±782,4708	96,630±10,264
2015	7714.286±1714.28	min.0	min.-0	min.-0	min.-0	min.-0	0	0
	min.-0; max.-12000	max.-150	Max.-18000	Max.-276.9230769	max.-21000	max.-228,260869565217	18000	216,8674699
		108.9245±20.434	9052.632±754.9977	138.288±13.8299	7083,333±1177,171	94,585±16,381	7117,647±770,1711	97,174531±10,912827
2016	8000±1333.33	0	min.-2000	min.-27.77777778	1000	min.-11,9047619047619	0	0
	min.-0; max.-12000	210.5263158	Max.-12000	Max.-230.7692308	12000	173,9130435	12000	206,8965517
		109.157±25.628	9473.684±928.3338	139.700±15.930	10857±1142,857	141,58765±19,6690	7783,784±738,4091	108,666±10,710
2017	7000±1812.378	0	min.-0	min.-0	4000	62,5	0	0
	min.-0; max.-12000	218.1818182	Max.-12000	Max.-230.7692308	12000	230,7692308	12000	222,2222222
		115.56±25.64	10500±718.7953	162.169789±15.24	8000±1632,993	113,784±23,796680	8829,268±608,7797	121,051±9,274
2018	7666.667±1498.147	48.7804878	min.-4000	min.-50	4000	71,42857143	0	0
	min.-4000; max.-12000	218.1818182	Max.-12000	Max.-250	12000	179,1044776	12000	266,6666667
		228.568±17.026	10000±921.1324	159.8270±17.785	12000±0	167,63±14,623	9575,758±694,99	163,03±53,01
2019	12000±0	146.3414634	min.-4000	min.-50	12000	117,6470588	0	67,79661017
	min.-1200; max.-12000	272.7272727	Max.-12000	Max.-255.3191489	12000	214,2857143	16000	369,2307692
	8800±1959.592	182.0606±66.6667	9428.5711±796.3811	143,23968±15.890240	12000±3346,64	163,03896±53,0120	10068,9655±833,3135	133,65948±13,419978
2020	4000	45.53996015	min.-4000	min.-62.5	4000	67,79661017	0	0
	12000	272.7272727	Max.-12000	Max.-255.3191489	24000	369,2307692	24000	358,2089552
	Mean-8563.464	Mean-137.1222319	Mean-8772.165508	Mean-134.5864666	16794,94417	125,6737881	8000,311	109,1827474
	Standard Error-401.735	St. Error-11.38233924	St. Error-470.3796015	Standard Error-6.835468445	7346,059066	6,802784082	317,8241108	6,206130053
	Minimum-6714.28	Minimum-96.9975463 Max.-228.568	Minimum-5050 Max.-228.568	Minimum-82.46248 Max.-162.1698	6700	90,5294	6666,667	90,1

Max.-12000

Table 5. ESAs mean doses in male patients

Year	ESA mean weekly dose (IU) in male patients receiving ESA before HD (group A)	ESA mean weekly dose (IU/kg) in male patients receiving ESA before HD per kg/weight (group A)	ESA mean weekly dose (IU) in male patients who were ESA treatment-naïve before HD (group B)	ESA mean weekly dose (IU/kg) in male patients who were ESA treatment-naïve before HD (group B)
2009	9750±2136.001 min.-2000 max.-19000	126.7959±27.526 min.-17.69912; max.-243.5897	7282.051±768.122 min.-0 max.-20000	94.72±9.64 min.-0 max.-225
2010	9428.571±2458.5 min.-2000 max.-19000	122.05±31.30962 min.-17.699; max.-243.52	6666.667±1007.451 min.-0 max.-19000	90,1036±15,236 min.-0 max.-330,4348
2011	9000±2569.047 min.-2000 max.-18000	132.627916±44.30332765 min.-23.255; max.-290.3226	8714.286±866.577 min.-2000 max.-18000	112.26252±10.785230 min.-28.571; max.-238095
2012	6700±1085.766 min.-0 max.-12000	90.52945±17.1072 min.-0 max.-193.548387096774	7205.125±556.1331 min.-0 max.-12000	91.70±7.21373 min.-0 max.-184.61538461

2013	9750±1472.971 min.-0 max.-12000	127,420376793965±21,83873 min.-0 max.-193,55	7000±768.42 min.-0 max.-12000	9.,0820750±10.39 min.-0 max.-222.222
2014	9571.429±1411.806 min.-2000 max.-12000	117.070624696326±18.5228874 min.-23.8095238095238 max.-176.470588235294	8428.571±757.35 min.-0 max.-12000	107.11796856±9.7691677 min.-0 max.-184.6154
2015	9400±1857.118 min.-0 max.-21000	110,97196710561±20,4767680 min.-0 max.-228.260869565217	7333.333±782.4708 min.-0 Max.-18000	96.630±10.264 min.-0 Max.-216.8674699
2016	7083.333±1177.171 min.-1000 12000	94.585±16.381 min.-11.9047619047619 173.9130435	7117.647±770.1711 min.-0 Max.-12000	97.174531±10.912827 min.-0 Max.-206.8965517
2017	10857±1142.857 min.-4000 max.-12000	141.58765±19.6690 min.-62.5 max.-230.7692308	7783.784±738.4091 min.-0 Max.-12000	108.666±10.710 min.-0 Max.-222,2222222
2018	8000±1632.993 min.-4000 max.-12000	113.784±23.796680 min.-71.42857143 max.-179.1044776	8829.268±608.7797 min.-0 Max.-12000	121.051±9.274 min.-0 Max.-266.6666667
2019	12000±0 min.-12000 max.-12000	167.63±14.623 min.-117.6470588 max.-214.2857143	9575.758±694.99 min.-0 Max.-16000	163,03±53.01 min.-67.79661017 Max.-369.2307692
2020	12000±3346.64 min.-4000 max.-24000	163.03896±53.0120 min.-67.79661017 max.-369.2307692	10068.9655±833.3135 min.-0 Max.-24000	133.65948±13.419978 min.-0 Max.-358.2089552
	Mean-16794.94417 Standard Error-7346.059066 Minimum-6700 Maximum-97427.571	Mean-125.6737881 Standard Error -6.802784082 min.-90.5294 max.-167.63	Mean-8000.311 Standard Error 317.8241108 min.-6666.667 Max.-10068	Mean-109.1827474 Standard Error 6.206130053 min.-90.1 Max.-163.03

Conclusion

It is necessary to expand the scope, follow-up and treatment in patients with nephrological diseases without waiting for the progression of the chronic kidney disease. When applying ESA, always take into account the sex of the patients and the specific characteristics of the female patients.

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