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FACULTY OF MEDICINE

DEPARTMENT "NEPHROLOGY, HAEMATOLOGY AND GASTROENTEROLOGY"

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„ANAEMIA AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS AND CONSERVATIVE TREATMENT"

PhD THESIS SUMMARY

FOR AWARDING OF EDUCATIONAL AND SCIENTIFIC DEGREE "**DOCTOR**"

Research supervisor:
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The dissertation is written on 169 pages, 49 of which contain review of the literature, 8 – aim, tasks, material and methods, 87 – author research, 4 – conclusions, contributions, list of publications, based on the dissertation, 17 – bibliography. The bibliography contains 385 literature sources – 5 of which in Cyrillic and 380 – in Latin.

The dissertation is reviewed and accepted at an extended meeting of the Department council of Department "Nephrology, Haematology and Gastroenterology"(Order № 1683/15.06.2023) of the Rector of Medical University – Pleven with qualified specialists in Nephrology from MMA – Sofia, Clinic of Nephrology – Prof. Rayna Teodosieva Robeva, MD, and Medical University – Sofia, Department of Nephrology of UMHAT "Tsaritsa Yoanna – ISUL" – Prof. Boryana Petrova Deliyska, MD, at 19.07.2023.

The PhD student is enrolled at 21.10.2019, at Department "Nephrology, Haematology and Gastroenterology" (Order № 3072/23.10.2019 of the Rector of Medical University – Pleven).

ABBREVIATIONS

BKD	Severity of chronic kidney disease
BP	Body pain
CGF	Cognitive function
ClCr	Creatinine clearance
DSE	Support from medical staff
EFKD	Reflection of chronic kidney disease
Epo	Erythropoietin (epoietin)
EWB	Emotional well being
FF	Physical function
GHP	General health perception
Hct	Hematocrit
Hg	Haemoglobin
MPEG	Methoxypolyethylene glycol
PST	Patient satisfaction
QSl	Quality of social life
RBC	Erythrocytes
RL	Physical functional role
RLE	Emotional functional role
Scr	Serum creatinine
SF	Social function
SL	Symptoms
SLP	Quality of sleep
SS	Social support
SXF	Quality of sexual function
TSAT	Transferrin saturation
VEF	Vitality
WS	Working status
ADPKD	Autosomal Dominant Polycystic Kidney Disease
RRT	Renal replacement therapy
RF	Renal function
CAKUT	Congenital anomalies of the kidney and urinary tract
GRF	Glomerular filtration rate
DN	Diabetic nephropathy
ESA	Erythropoiesis stimulating agent
PD	Peritoneal dialysis
RA	Renal anemia
BW	Body weight
CKD	Chronic kidney disease
CRF	Chronic renal failure
CGN	Chronic glomerulonephritis
HD	Haemodialysis
HDT	Haemodialysis treatment
CIN	Chronic interstitial nephritis
HN	Hypertensive nephropathy
CPN	Chronic pyelonephritis

1. Introduction

Anaemia is a common complication of chronic renal failure/chronic kidney disease and is associated with decreased quality of life, accelerates the progression of chronic kidney disease, causes increase in morbidity and frequency of hospitalizations, leads to decrease of life expectancy and increase of mortality.

Data from clinical researches shows that renal anemia can be present in around 2/3 of the patients with renal dysfunction. With the progression of chronic renal failure, the frequency of anemia increases and affects almost all patients with chronic kidney disease stage 5.

The main reason for anemia in chronic renal failure is the reduced synthesis of endogenous erythropoietin, but the correlation between severity of chronic renal failure and severity of anemia is not well defined.

After 1990, when treatment with human recombinant erythropoietin was introduced in clinical practice, treatment of renal anemia underwent a massive progress. That way epoietin and the following erythropoiesis stimulating agents generally improved the symptoms and prognosis of patients with chronic kidney disease. During this long period of time ESA affirmed as effective drugs and nowadays remain the golden standard for treatment of renal anemia. Despite the advantages of the erythropoietin therapy and the presence of different clinical guidelines, the treatment of anemia in patients with CRF is defined as unsatisfactory.

There is a continuous interest in studying and treatment of renal anemia in patients with chronic renal failure. Unfortunately, there are very few studies of anemia related to chronic renal failure, and the studies on anemia in predialysis stage have been defined as “insufficient”.

2. Aim and tasks of the dissertation

Aim:

To evaluate the treatment of renal anemia in patients with CKD – in predialysis stage and on dialysis treatment and to analyze the data about social and demographical structure of researched groups, leading kidney diseases, severity of CKD, used ESA, effectiveness of treatment and its impact on the quality of life.

Tasks:

1. To make a socio-demographical characteristics of treated patients with CKD in predialysis and during dialysis treatment.
2. To evaluate and analyze the connection between age, gender and leading kidney disease with severity of anemia and CKD.
3. To analyze treatment of renal anemia in predialysis period by defining its effectiveness and comparing the effectiveness of the application of different ESA.
4. To analyze treatment of renal anemia during hemodialysis treatment of CKD, by defining its effectiveness and comparing results of application of different ESA.
5. To analyze treatment of renal anemia during treatment of CKD with peritoneal dialysis, by defining its effectiveness and comparing the effectiveness of application of different ESA.
6. To compare the results of treatment of renal anemia during hemodialysis and peritoneal dialysis treatment.
7. To evaluate the quality of life in patients with CKD in predialysis stage and analyze the changes after correction of renal anemia.
8. To evaluate quality of life in patients with CKD, undergoing renal replacement therapy with dialysis.

3. Material and methods

3.1 Material

The research includes patients with CKD, who underwent treatment in Clinic of Nephrology and Dialysis at University Hospital “Dr. Georgi Stranski”, Pleven in the period from 2012 to 2021.

Patients are divided in several major groups:

3.1.1. Evaluation of treatment of renal anemia with ESA:

a) patients with CKD I-IV stage, who underwent conservative treatment of chronic renal failure and renal anemia (predialysis stage) – total 642 patients;

b) patients with CKD V stage, who underwent treatment of chronic renal failure with extracorporeal blood purification methods: hemodialysis – 204 and peritoneal dialysis – 51 patients, and treatment of renal anemia simultaneously – total 255 patients.

3.1.2. Evaluation of quality of life:

a) patients with CKD stage I-IV – 60;

b) patients with CKD stage V, treated with hemodialysis and peritoneal dialysis – 84.

All patients have declared their consent for participation in the evaluation of quality of life and have filled a questionnaire.

3.2 Methods of diagnosis and treatment.

3.2.1. Of CKD and renal anemia.

Methods of diagnosis are anamnesis, physical examination, laboratory markers: a) blood – hemoglobin, hematocrit, erythrocytes, erythrocyte indices, leucocytes, thrombocytes, serum urea, creatinine, uric acid, sodium, potassium, calcium, phosphorus, total protein and albumin, glucose and when indicated – blood sugar profile, blood gas analysis, when indicated – enzymes, markers of

hemostasis, lipid profile, fibrinogen, C-reactive protein; b) imaging methods – abdominal ultrasound, echocardiography, native and contrast X-ray and computer tomography. Glomerular filtration is defined as creatinine clearance calculated using the formulas MDRD (Modification of Diet in Renal Disease) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

Treatment of chronic renal failure in predialysis period is performed with different medication, depending on its severity and for renal anemia – with different erythropoiesis stimulating agents, approved for use in Bulgaria and present on the market: Epoetin alfa (Eprex, Binocrit), Epoetin beta (NeoRecormon), Epoetin zeta (Retacrit), Methoxypolyethylene glycol-epoetin beta (Mircera), Darbepoetin alfa (Aranesp); iron-containing drugs for oral and parenteral use. Application of ESA in patients in predialysis was subcutaneous, and of the iron drugs – intravenous and oral. Treatment of anemia in the dialysis period is performed with recombinant erythropoietin, which was applied intravenously in patients undergoing treatment with hemodialysis and subcutaneously – in patients undergoing treatment with peritoneal dialysis.

3.2.2. For quality of life assessment.

A total of three cross-section studies were conducted, using a validated, worldwide accepted questionnaire, which evaluates the quality of life. This research was conducted in 2021 and 2022.

The first study evaluates patients with CKD in predialysis period with renal anemia, who have been questioned twice – at the beginning of renal anemia treatment and six months after that. The second study evaluates patients with CKD undergoing treatment with hemodialysis.

The questionnaire survey was performed using the specialized organ specific questionnaire KDQOL-SF-36™.

The questionnaire has been created and validated by RAND Corporation™ in 1999, and its latest version “v 1.3” has been

updated in 2015. KDQOL-SF-36™ contains one main panel with 8 domains and a second, additional panel, which is organ specific for patients with renal diseases and patients undergoing dialysis treatment, and contains a total of 11 domains:

The questionnaire is approved by KENID at MU-Pleven (Decision №685/2022)

TRANSLATION, VALIDATION AND ADAPTION OF ORGAN SPECIFIC QUESTIONNAIRE FOR EVALUATION OF QUALITY OF LIFE – KDQOL-SF-36™ FOR PATIENTS WITH RENAL DISEASES.

The English version of KDQOL-SF_36™, developed and affirmed by RAND-Corporation™, is available for free. The author's rights, application and validation in other languages are also their ownership. After obtaining a written consent from the corporation, the following steps of the standard methodology for translation and validation of the questionnaire were performed.

3.2.3 Methods for statistical analysis.

The acquired primary information from the clinical monitoring and medical documentation is processed using statistical software packages SPSS for Windows, v. 23 and Microsoft Office Excel 2013.

A descriptive analysis has been performed, and the frequency distribution of the variable are presented in tables. The quantitive variables are described with their average values and standard deviations. The qualitive variables are presented with relative shares of their categories.

The test of Kolmogorov-Smirnoff is used to check the form of distribution of quantitive variables, and based on it proper parametric and non-parametric methods of analysis have been chosen.

Verification of hypothesis about the presence of statistically significant difference between average values of quantitive indicators in patients, treated with the same drug in different periods of treatment are performed: between two periods using Fisher's t-test for subordinate samples and using Wilcoxon signed-rank test; between three and more periods – with single-factor analysis of variance ANOVA for repetitive evaluations and Friedman's test.

In the testing of hypothesis for the presence of statistically significant differences in the average values of quantitive variables between two independent samples a Fisher's t-test is used for independent samples and Mann-Whitney's test, and for more than two independent samples the single-factor analysis of variance ANOVA and Kruskal-Wallis tests are used.

Correlation analysis with definition of correlation coefficient of Pearson (r) or Spearman (r_s) is used for evaluation of the presence of correlation between the variables and evaluation of the strength of the connection.

Graphical analysis is used for visualization of the results.

Hypothesis testing is performed at level of significance of the zero hypothesis α=0,05.

4. OWN RESEARCHES

4.1. Treatment of renal anemia with erythropoiesis stimulating agents in patients with chronic kidney disease in predialysis stage.

4.1.1. Social-demographical characteristics of treated patients with CKD in predialysis stage.

The evaluated group includes 642 patients with CKD stage 1-4, who underwent treatment of renal anemia with ESA from 2008 to 2022. Female patients are 348 (54,2%), male patients – 294 (45,8%) (tabl. №1). Overall females are 54 (8,4%) more than males, which is probably connected to the larger number of females with renal diseases in general. There are no significant differences in the gender structure in the patient groups, treated with different ESAs (p=0,665).

Table №1. Patients, treated with different ESAs in predialysis (n=642).

	Epo alpha	Epo beta	Epo zeta	MPEG Epo beta	DarbEpo alpha	Total
Female	150	67	81	34	16	348 (54,2%)
Male	130	58	58	28	20	294 (45,8%)
Total	280	125	139	62	36	**642**

Comparison between the treated with the two main types of ESA shows that treatment of RA is performed mainly with rapid-acting ESA – in 84,7% of the patients. Data analysis for used ESAs, distributed by gender, shows similar relative share, with insignificant differences ($\chi 2$=0,472; p=0,492).

Data analysis shows that initiated treatment of RA with the five ESAs in 642 patients continued in the following 6 months in 447 (69,6%) of them and continued for 12 months in 318 (49,5%).

Age distribution of patients by decades at the time of treatment initiation of renal anemia (tabl. №4) shows that most of them are in the age interval between 71-80 years – 242 patients (37,7%), followed by the group 61-70 years – 182 patients (28,3%). This actually shows that CKD and renal anemia develop most frequently in the age group from 61 to 80 years – in 66,0% of all treated patients.

Table №4. Distribution of patients by age at the beginning of treatment of RA with ESA (n=642).

Age (years)	Number patients	Rel. variab.
20-40	18	2,8%
41-50	37	5,8%
51-60	71	11,1%
61-70	**182**	**28,3%**
71-80	**242**	**37,7%**
Above 80	92	14,3%
Total	642	100,0%

4.1.2. Comparison of the number of treated and number of issued protocols – in total and for different ESA.

For the reviewed period of time a total of 2535 protocols for treatment with ESA have been issued for all 642 patients. Each protocol is valid for and respectively provides treatment for 6 months. This allows us to calculate that the total duration of treatment for the whole evaluated group of 642 patients is 1 267,5 patient years.

The largest number of protocols were issued for treatment with Epo beta and the largest number of patients were treated with Epo

alpha. The juxtaposition of the number of issued protocols with the number of treated with each drug shows that on average a patient has received the most protocols for treatment with Epo beta – 6,8 and MPEG Epo beta – 5,7, and the fewest with DarbEpo alfa – 2,3 (tabl. №6). The observed differences in the average number of protocols for different medications are statistically credible (p=0,001).

Table №6. Comparison between the number of patients and issued protocols for treatment with each drug.

	Epo alpha	Epo beta	Epo zeta	MPEG Epo beta	DarbEpo alpha	Total
Protocols (number)	811	856	428	356	84	**2535**
Patients	280	125	139	62	36	**642**
Average number of protocols per patient	2,9	6,8	3,1	5,7	2,3	**3,9**

This way the average period of treatment is the longest for Epo beta – 41,1 months, and the shortest for DarbEpo alpha – 14,0 months. The average period of treatment of anemia in predialysis stage with all drugs is 23,7 months (fig. №5).

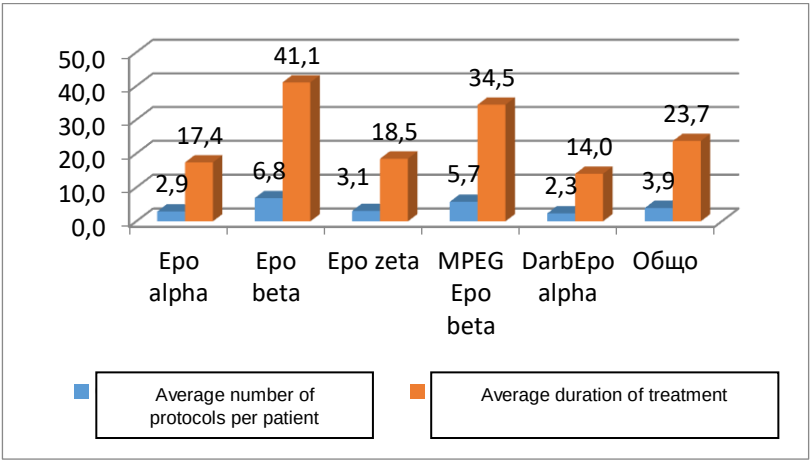

Figure №5. Comparison between the average number of protocols per patient and the average duration of treatment with each drug.

Table №7. Distribution of patients based on the number of issued protocols per patient (n=642).

Protocols per person	Epo alpha - Nr. patients	Epo alpha - in %	Epo beta - Nr. patients	Epo beta - in %	Epo zeta - Nr. patients	Epo zeta - in %	MPEG Epo beta - Nr. patients	MPEG Epo beta - in %	Darb-Epo alpha-Nr. patients	Darb-Epo alpha - in %	Total Nr. patients	Total in %
1	111	39,6	18	14,4	44	31,7	10	16,1	12	33,3	195	27,0
2	56	20,0	15	12,0	37	26,6	8	12,9	13	36,1	129	21,5
3	28	10,0	6	4,8	15	10,8	2	3,2	4	11,1	55	8,0
4	28	10,0	11	8,8	15	10,8	9	14,5	6	16,7	69	12,2
5	13	4,6	13	10,4	6	4,3	7	11,3		0,0	39	6,1
6	19	6,8	6	4,8	5	3,6	3	4,8		0,0	33	4,0
7	6	2,1	5	4,0	4	2,9	4	6,5		0,0	19	3,1
8	4	1,4	8	6,4	5	3,6	4	6,5		0,0	21	3,6
9	11	3,9	13	10,4	3	2,2	5	8,1		0,0	32	4,9
10	4	1,4	6	4,8	5	3,6	1	1,6	1	2,8	17	2,8

11			3	2,4			3	4,8			6	1,4
12			1	0,8			3	4,8			4	1,1
13			3	2,4				0,0			3	0,5
14			4	3,2				0,0			4	0,6
15			0	0,0				0,0			0	0,0
16			4	3,2			2	3,2			6	1,3
17			0	0,0				0,0			0	0,0
18			6	4,8				0,0			6	1,0
19			3	2,4			1	1,6			4	0,8
Total	280	100,0	125	100,0	139	100,0	62	100,0	36	100,0	642	100,0

Detailed analysis of data about the distribution of patients based on the number of protocols issued per person, shows that every fourth patient is treated with ESA in a period of only 6 months. Two protocols received 21,5% of patients, a total of 20,2% - 3 or 4 protocols. From 5 to 10 protocols received 24,6%, and the remaining 6,7% (33 patients) received protocols for period of 5 to 9,7 years (tabl. №7).

Among treated with rapid-acting ESA the largest relative share of patients who received one protocol for treatment of RA in the group of treated with Epo alpha – 111/280, 39,6% and with Epo zeta – 44/139, 31,7%. In the group of treated with Epo beta one protocol for treatment received only 18/125, 14,4%. The difference of the indicators of the other two recombinant erythropoietin drugs is significant ($p<0,001$), and by adding the data that 49,6% of treated with Epo beta received from 6 to 19 protocols, we can conclude that treatment with this drug is the longest, respectively – the most successful and most effective (tabl. №7).

4.1.3. Evaluation of the severity of anemia before initiation and during treatment with different ESAs.

For evaluation of the severity of anemia depending on the severity of CKD/CRF, measured by eGFR, patients are divided into groups in interval 10 ml/min/1,72 m^2.

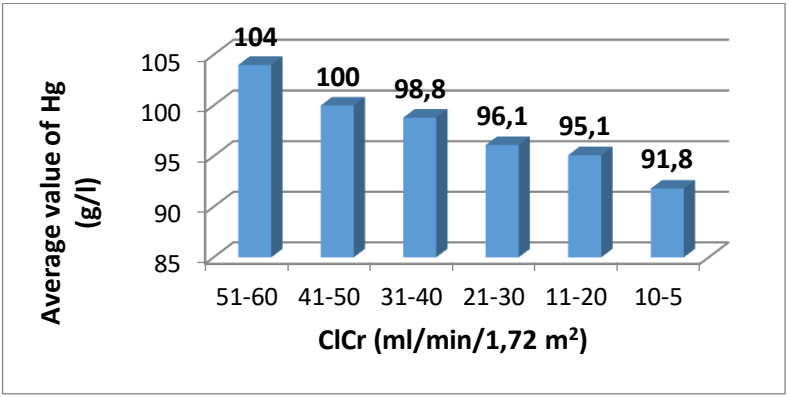

Figure №7. Average value of hemoglobin in different severity of CKD, evaluated using measured eGRF (N=642).

A gradual, linear decrease is found in the average hemoglobin value from 104,0±13,3 g/l in eGFR 51-60 ml/min/1,72m^2 to 91,8±12,6 g/l in eGFR 10-5 ml/min/1,72m^2.

Average values of hemoglobin are almost equal for patients from both genders and in each subgroup – distributed by drugs and respectively before and after 6-month treatment – all differences are less than 1 g/l. The average increase in the hemoglobin value after 6-month treatment varies from 6,8 to 18,3 g/l in the groups treated with different drugs, respectively the average increase for a month is from 1,1 to 3,1 g/l (tabl. №8).

Table №8. Hemoglobin values at the beginning of treatment and after 6 months.

	Epo alpha	Epo beta	Epo zeta	MPEG Epo beta	DarbEpo alpha
Hg – before treatment - female (g/L)	94,3±10,9	99,3±11,3	98,2±12,4	105,6±8,6	102,3±8,5
Hg – before treatment - male(g/L)	92,2±10,0	98,8±14,2	98,2±13,1	106,9±12,3	103,0±5,5
Total (n=642)	**93,3±10,5**	**99,1±12,7**	**98,2±12,6**	**106,2±10,4**	**102,6±6,9**
Hg – post 6-month treatment - female (g/L)	110,7±11,4	117,1±10,8	109,9±13,6	109,9±12,6	113,8±6,5
Hg – post 6-month treatment - male(g/L)	109,8±11,9	117,7±13,1	108,8±14,6	116,9±10,5	115,8±9,0
Total (n=447)	**110,3±12,2**	**117,4±11,9**	**109,9±13,5**	**113,0±10,1**	**115,0±8,1**
Average difference (g/L)	17,0	18,3	11,7	6,8	12,4
Average Hg increase per month (g/L)	2,8	3,1	2,0	1,1	2,1
p	0,001	0,001	0,001	0,002	0,001

Additional evaluation of the markers allows us to conclude, that anemia is corrected most effectively and significant in patients treated with Epoetin beta.

Comparison of the average values of hemoglobin in the period of supportive treatment of anemia, respectively in the first 6 months and after the 12th month, shows stable level of hemoglobin, and the reference range, for treated with all ESA. For three of the drugs the average value of hemoglobin has an average increase for a period of 12 until over 48 months between 0,3 and 1,1 g/l, and for two of them – average decrease with 3,7 and 4,3 g/l. Despite that decrease in these groups, the average value of hemoglobin remains within the target reference range (tabl. №9).

Table №9. Hemoglobin values after 6 months and 12 months of treatment.

	Epo alpha	Epo beta	Epo zeta	MPEG Epo beta	DarbEpo alpha
Hg – post 6-month treatment - female(g/L)	110,7±11,4	117,1±10,8	109,9±13,6	109,9±12,6	113,8±6,5
Hg – post 6-month treatment - male (g/L)	109,8±11,9	117,7±13,1	108,8±14,6	116,9±10,5	115,8±9,0
Total	**110,3±12,2**	**117,4±11,9**	**109,9±13,5**	**113,0±10,1**	**115,0±8,1**
Hg – post 12-month treatment - female (g/L)	111,7±10,2	112,6±10,9	111,5±12,0	112,6±8,3	113,3±7,8
Hg – post 12-month treatment - male (g/L)	107,7±13,5	113,8±10,4	107,9±12,9	115,7±8,0	109,0±6,5
Total	**110,6±11,4**	**113,1±10,4**	**110,4±12,3**	**114,1±8,3**	**111,3±7,4**
Average difference	0,3	-4,3	0,5	1,1	-3,7
p	0,114	0,005	0,101	0,877	0,094

4.1.5. Evaluation of the treatment of RA with different ESAs.

The average weekly doses of Epo alpha and Epo zeta during the first 6-month period are similar, but the dose od Epo beta is lower. The average monthly doses of both long-acting ESAs are completely comparable for the same period of time. We found a credible decrease in the average monthly doses of all drugs during the second 6-month period of treatment of RA (tabl. №14).

Table №14. Doses of different ESAs during the first and second 6-month period of treatment.

	Epo alpha (UI/weekly)	Epo beta (UI/weekly)	Epo zeta (UI/weekly)	MPEG Epo beta (mcg/mon.)	DarbEpo alpha (mcg/mon.)
Dose, 1st 6-month period - female	6643±1874	6358±2220	6875±2268	106,6±48,2	105,0±20,0
Dose, 1st 6-month period - male	7423±1751	6310±2369	7322±1978	92,0±29,7	99,0±25,5
Total	**7005±1856**	**6336±2281**	**7065±2153**	**100,0±41,2**	**101,7±23,1**
Dose, 2nd 6-month period - female	5395±2438	5017±2371	5822±2424	94,8±33,7	86,7±26,5
Dose, 2nd 6-month period - male	5838±2245	4510±2308	6694±2447	79,6±25,3	86,7±36,8
Total	**5589±2359**	**4785±2345**	**6153±2372**	**88,1±30,9**	**86,7±32,7**
Average difference	**-1416**	**-1551**	**-912**	**-11,9**	**-18,3**
Average difference (in %)	20,2	24,5	12,9	11,9	17,4
p	< 0,001	< 0,001	< 0,001	< 0,05	< 0,001

The average doses of four of ESAs additionally decrease in the period of treatment after the 12th month, and the change in the doses of Epo alpha and Epo zeta – credibly, and the other three drugs – uncredible (tabl. №15).

Tabe №15. Doses of different ESAs during the second 6-month period of treatment and after the 12th month.

	Epo alpha (UI/weekly)	Epo beta (UI/weekly)	Epo zeta (UI/weekly)	MPEG Epo beta (mcg/mon.)	DarbEpo alpha (mcg/mon.)
Dose, 2nd 6-month period - female	5395±2438	5017±2371	5822±2424	94,8±33,7	86,7±26,5
Dose, 2nd 6-month period - male	5838±2245	4510±2308	6694±2447	79,6±25,3	86,7±36,8
Total	**5589±2359**	**4785±2345**	**6153±2372**	**88,1±30,9**	**86,7±32,7**
Dose, 13-60 months - female	4132±2383	4336±2471	4795±2519	83,9±39,5	83,1±18,0
Dose, 13-60 months - male	5100±2694	3403±2000	6473±2364	62,1±24,4	107,3±22,4
Total	**4399±2507**	**3935±1973**	**5271±2584**	**73,5±34,9**	**94,2±23,2**
Average difference	-1190	-850	-882	-14,6	+8,7
p	0,001	0,574	0,005	0,501	0,217

The average monthly dose of MPEG Epo beta decreases credibly at the sixth and 12th month. The average monthly dose of DarbEpo alpha decreases credibly at the 6th month, but after that increases at the 12th month, which can not be explained.

4.1.6. Evaluation of renal function in treatment of RA.

At the time of initiation of treatment of RA with different ESAs the average value of serum creatinine varies from 236,4±84,9 to 285,7±144,1 mcmol/l. After six months of treatment the average value of serum creatinine varies in different therapeutic groups from 239,4±115,6 to 331,3±173,3 mcmol/l. That way in the groups treated with Epo alpha and Epo beta the average value of serum creatinine decreases, and increases in the other three. The differences vary from -29 to +58 mcmol/l. The changes in the average values of serum creatinine are credible only in the group

treated with DarbEpo alpha. After 12 months of treatment of RA the average values of serum creatinine vary between the groups from 251,2±121,5 to 306,8±147,1 mcmol/l. The difference between the average values at the 12th and the 6th month vary from -28,7 to +28,5 mcmol/l. The groups in which the serum creatinine decreases are three and in two of them the serum creatinine has had increased in the previous comparison of the dynamics of RF. That way there is an enduring trend for decrease of the average value of serum creatinine from the beginning to the end of treatment only in patients, treated with Epo alpha. Decrease in serum creatinine is found in 5/10 comparisons, and in the others – increase. Analysis of the state of RF, evaluated with the values of calculated creatinine clearace at the beginning of treatment of RA shows that in the five therapeutic groups its average value maches fourth stage CKD and varies in very narrow values from 20,9±11,1 to 26,1±13,7 ml/min/1,72m^2. After six monnth treatment the average values of clearance vary from 20,9±11,3 to 26,9±13,0 ml/min/1,72m^2. Analysis of the change in creatinine clearance after six month treatment of RA shows that its average value has increased from 0,6 to 2,4 ml/min/1,72m^2 in the groups treated with Epo alpha, Epo beta and MPEG Epo beta and is decreased with 0,9 and 5,1 ml/min/1,72m^2 in the other two groups. After the treatment of RA has continued for more than 12 months in the five therapeutic groups the average value matches the same fourth stage CKD (same as before treatment initiation) and again varies in very narrow borders from 19,6±9,4 to 24,1±13,2 ml/min/1,72m^2.

Analysis of the change in creatinine clearance after more than 12 months of treatment of RA shows that its average value decreases with 0,4 to 3,3 ml/min/1,72m^2 in the gruops treated with Epo alpha, Epo beta and MPEG Epo beta (the same for which an incresed has been recorded after 6 months of treatment) and is increased with 1,6 and 3,1 ml/min/1,72m^2 in the other groups.

The overall analysis of the dynamis of creatinine clearance shows that regardless of the serum creatinine, none of the therapeutic

groups shows one-way changes during the three analyzed periods. At the same time RF remains relatiely stable and most of total 15 compared average values are in the interval from 20,0 to 25,0 ml/min/1,72m^2. Important role has the fact that the average value of creatinine clearance in both groups – treated with Epo alpha and Epo zeta, is higher after treatment for more than 12 months, compared to that before initiation of therapy.

That way summarized evaluation of RF through an analysis of the changes of serum creatinine and calculated creatinine clearance in different therapeutic groups shows that after 6 and 12-month treatment of RA with ESAs there are different changes – both improvement and decline in the RF. Overall we can summarize that there is no significant declining in the RF – serum creatinine remains in values below 300 mcmol/l in four therapeutic groups with the most patients, and the creatinine clearance remains in values above 20 ml/min/1,72m^2 in 14/15 comparisons.

4.1.7. Treatment of RA in patients with differet main renal diseases.

The distribution of patients, who undergo treatment of RA in predialysis stage, based on their main renal disease show that most of them are with hypertensive and diabetic nephropathy (fig. №8). The relative share of patients with these two diseases is 59,8%. These data also shows that the most common causes for development of CKD/CRF are exactly these two chronic nephropathies.

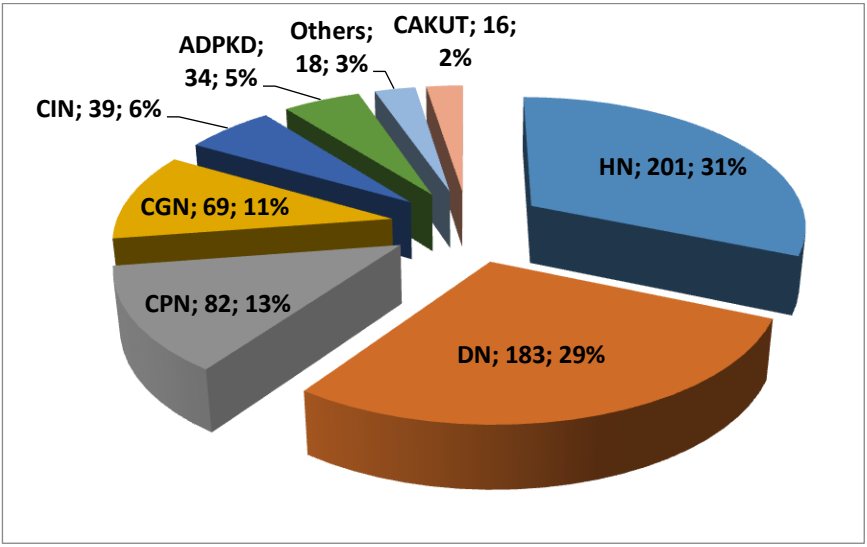

Figure №8. Distribution of patients with different chronic nephropathies during the first 6-month period of treatment (n=642).

Comparison between the average values of hemoglobin in the different groups with different main disease during the three periods of treatment shows that the start hemoglobin in patients who do not have ADPKD varies in very narrow ranges between 95,7±11,8 g/l. There are small differences between the same patient groups during the second 6-month period – from 110,1±14,4 to 112,9±11,9 g/l and during the period after the 12th month – from 111,5±16,7 to 113,4±10,1 g/l. Credibly higher are the average values of hemoglobin for the first two periods of treatment only in patients with ADPKD (tabl. №21). The average value in these patients even surpasses the upper range of the recommended target interval during the second 6-month period. This definitely supports the long known fact that in patients with ADPKD anemia in CKD is lighter.

Table №21. Values of hemoglobin during the three periods of treatment in patients with different main diseases.

Main disease	Hg (g/L) - first 6 months	Hg (g/L) - second 6 months	Hg (g/L) - after 12 months
ADPKD	103,4±17,7	126,7±12,2	111,0±11,1
DN	95,7±16,9	110,6±18,9	111,5±16,7
CGN	97,8±11,8	112,9±11,9	112,0±11,3
CIN	96,9±14,1	111,0±15,2	113,4±10,1
HN	96,0±11,1	113,2±10,8	111,7±11,8
CPN	96,6±13,0	110,1±14,4	112,2±9,9

Hemoglobin in patients from each group during the first 6 months increases and is significantly different from the values for the next two periods, whereas these differences are not noticed between the average values of hemoglobin in the second 6-month period and the period after 12 months.

All average values of hemoglobin after 6 months of treatment in all disease groups are in the target interval, defined by the Requirements of NHIF for treatment of anemia in the predialysis period.

Comparison between the average levels of serum creatinine during the different periods of treatment of RA for each disease group show insignificant differences, with the exclusion of the levels in patients with CIN – there are statistically significant differences in the average level of creatinine between the first 6months and the one in the second 6 months (p=0,012) and between the level in the second 6 months and the average level in the period after 12 months (p=0,037).

The average levels of creatinine clearance show significant differences in the three periods in patients with CIN (p=0,002) and CPN (p=0,032). Both groups show credible differences in the levels

of creatinine clearance during the first 6 months and the period after 12 months.

In summary – the detailed analysis of the dynamics of serum creatinine and calculated creatinine clearance shows both significant and insignificant changes in time in the different disease groups. Both average values of the markers, as well as their changes give us reason to conclude that in some disease groups the renal function slightly improves, whereas in others – slignthly worsens, but remains in the frames of CKD stage 4.

4.1.8. Summary

1. Treatment of RA in predialysis is performed mainly with rapid-acting ESA – in 84,7% of the patients. Dynamics of changes of the number of patients in the groups treated with different ESA in time is similar.

2. The mean age of patients at the time of initiation of treatment with recombinant, rapid-acting epoetins varies from 66,6 to 72,1 years. Patients treated with long-acting ESA are younger, their average age is from 63,1 to 70,4 years.

3. Treatment of RA in predialysis is performed most commonly on patients in the age interval between 71-80 years (37,7%), followed by patients aged between 61 and 70 years (28,3%) these data allows us to conclude that most commonly CKD and renal anemia develop in the age group between 61 and 80 years – in 66,0% of the analyzed patients.

4. Analysis of the correlation “age-treatment with ESA for more than 12 months” shows that treatment of RA is performed primarily in patients aged over 60 years – with 83,5% from the issued protocols. Most protocols – 59,8% in the period after 12 month received patients above 70 years old.

5. The average duration of treatment of anemia in predialysis in all drugs is 23,7 months. The average duration of treatment is the

longest for Epo beta – 41,1 months and the shortest for DarbEpo alpha – 14,0 months. Results, showing that 49,6% of treated with Epo beta received 6 to 19 protocols, allow us to conclude that treatment with this drug is the most continuous, respectively – most successful and most effective.

6. Results from the study confirm the connection between RF and anemia. A continuous, lineary decrease of the average value of hemoglobin from 104±13,3 g/l in patients with eGRF 51-60 ml/min/1,72m2 to 91,8±12,6 g/l in eGRF 10-5 ml/min/1,72m2.

7. The average increase of the value of serum hemoglobin in the groups, treated with different ESAs, after 6-month treatment varies from 6,8 to 18,3 g/l, respectively the average increase is from 1,1 to 3,1 g/l monthly. The average values of hemoglobin in the period of supportive treatment of anemia are in the reference range in treated in predialysis with all ESAs.

8. The average weekly doses of Epo alpha and Epo zeta during the first 6-month period are similar, and the dose of Epo beta is lower. Completely comparable are the average monthly doses of both long-acting ESAs. There is a credible decrease of the average monthly doses of all drugs during the second 6-month period of treatment of RA in predialysis and additional decrease in the period after 12^{th} month in four of the five drugs.

9. The summarized evaluation of RF through analysis of changes of serum creatinine level creatinine clearance in different therapeutic groups shows that after 6- and 12-month treatment of RA with ESA shows different changes – both improvement, as well as worsening of the RF. All in all, we can summarize that there is no significant worsening of the RF – the average values of serum creatinine remains below 300 mcmol/l in the four therapeutic groups with the most patients, and the average value of creatinine clearance remains above 20 ml/min/1,72m2 in 14/15 comparisons made.

10. The distribution of patients, in whom treatment of RA in predialysis was performed, by main disease shows that most of

them are with hypertensive and diabetic nephropathy with a total of 59,8%. This defines these two nephropathies as the leading causes for development of CKD/CRF. In the time of the survey and respectively of the treatment the order of chronic nephropathies as a reason for development of CKD/CRF doesn't change.

11. Correction of RA with ESA is effective in all patients with different main diseases. Hemoglobin in all etiological groups increases credibly in the first 6-month period of treatment.

4.2 TREATMENT OF RENAL ANEMIA WITH ESA IN PATIENTS WITH CKD UNDERGOING HEMODIALYSIS TREATMENT.

4.2.1. Social and demographical characteristics of the evaluated group.

The study is made using 204 patients with CKD stage 5 who started and are undergoing hemodialysis treatment for the period 2012-2021. Patients with CKD whose hemodialysis treatment lasted for less than 6 months were excluded from the study.

Distribution by gender shows that male patients – 117/204 are with 14,8% more than female patients. The average age of all patients at the time of hemodialysis start is 62,6±13,1 years. The average age of male patients is 60,6±14,1 years, and of female – 65,2±11,2 years, the difference is significant – $p<0,014$.

The duration of hemodialysis treatment until its termination or until the time of the study varies from 6 to 114 months, on the average 37,7±27,7 months. In female patients the average length of HDT is 34,3±24,1 months and in males – 40,3±29,2 months, the noticed differences are not statistically significant – $p=0,234$. That is why we can conclude that the average age of females at the start of HDT is significantly higher than in males, but the average duration of HDT is lower compared to the duration in males, despite the fact that the difference does not reach statistical significance.

Additional analysis of data shows that the duration of HDT has negative correlation with age (fig. №12). With the increase of the length of HDT the average age decreases (r=0,268, p=0,001), i. e. longer duration of HDT is reached only by younger patients. The difference between the average age of patients with the shortest (6-12 months) and longest (above 84 months) duration of HDT is 13,1 years and is statistically significant (p=0,001).

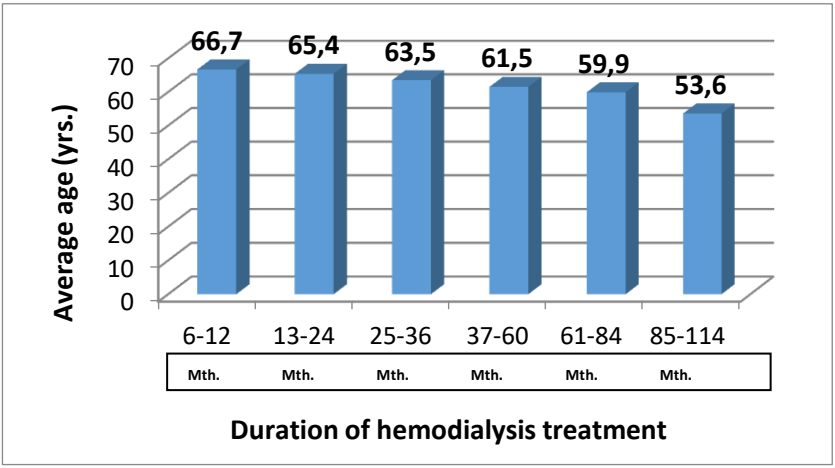

Figure №12. Values of the average age of patients in groups with different duration of hemodialysis treatment (n=204).

The correlation between duration of HDT and age is linear and is presented with the following equation:

Length of HDT (in months) = 73,61 - 0,268 x age.

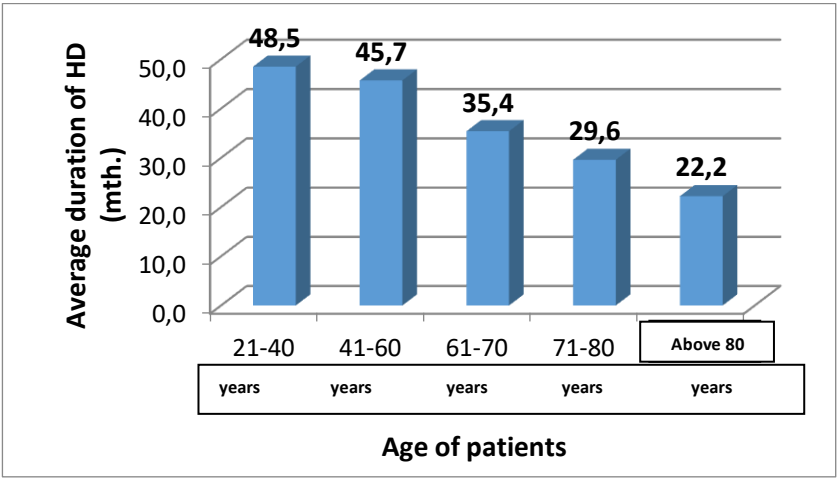

Figure №13. Correlation between patients' age and HDT length (n=204).

Analysis of the dependence between age and duration of HDT shows that younger patients (21-40 years) have more than twice as long average duration of HDT – 48,5±29,7 months, compared to the oldest patients (above 80 years) – 22,2±22,1 months (fig. №13). The differences found in the length of HDT in different ages are statistically significant (p=0,002).

4.2.2. Analysis of treatment of RA with ESAs at the beginning of hemodialysis treatment.

The treatment of RA of the evaluated group of 204 patients during the study period of 10 years is performed with only two drugs – Epoetin alpha and Epoetin beta. The distribution of patients based on the drug shows that the longer, respectively more patients underwent treatment with Epo alpha 122/204.

The weekly doses of ESA immediately after initiation of HDT for both drugs varied from 1000 to 9000 IU. This big difference is a result from the fact that some patients had undergone treatment in the predialysis period and right before the beginning of the organ

substituting treatment – in 75/204, which is why their initial doses are lower and correspond to the doses of supportive treatment.

Comparison between the average weekly doses of both drugs in total for both genders at the beginning of HDT shows that the average dose of Epo beta is 16% higher than the dose of Epo alpha (p=0,002). Comparison of these doses – both total weekly dose and weekly dose calculated on kg body weight show one-way significant differences (tabl. №26).

Table №26. Comparison between the initial weekly doses in treated with Epo alpha and Epo beta – total and per kg/BW (n=204).

	Epo alpha	Epo beta	Difference	p	Total
Average weekly dose (UI/weekly)	5848±2455	6970±2323	16%	0,002	6335±2462
Average BW (kg)	75,3±16,0	79,2±16,6	5%	0,094	76,8±16,3
Average weekly dose (UI/kgBW/weekly)	78	88	12%	0,044	82

4.2.3. Severity of anemia at the beginning of HDT.

At the beginning of HDT the value of Hg varies from 39 to 129 g/l. the distribution of patients based on the value of hemoglobin shows that in most of them 100/204 – 40% this value is between 81 and 100 g/l. In 38/204 patients – 18,6% anemia was extremely severe with hemoglobin value below 80 g/l (fig. №15).

Comparison between hemoglobin values in patients in the different age groups shows that despite the logical suspicion anemia is credibly more severe (p=0,019) in younger and less severe in patients aged between 71 and 80 years (tabl. №27).

Table №27. Comparison between the hemoglobin values, serum iron and TSAT in different age groups at initiation of hemodialysis treatment (n=204).

Age	Hemoglobin (g/L)	Ser. iron (mcmol/l)	TSAT (%)
21-40 years	87,5±20,2	11,1±7,4	27,4±15,9
41-60 years	90,3±15,7	12,0±6,4	28,4±12,9
61-70 years	95,4±15,0	10,1±5,1	25,7±9,5
71-80 years	99,0±15,3	9,2±4,8	23,6±11,1
Above 80 years	97,4±16,0	12,3±7,2	29,0±14,8

4.2.4. Severity of CKD at the beginning of HDT and RA treatment.

At the beginning of HDT the value of serum creatinine varies from 500 to 2800 mcmol/l.

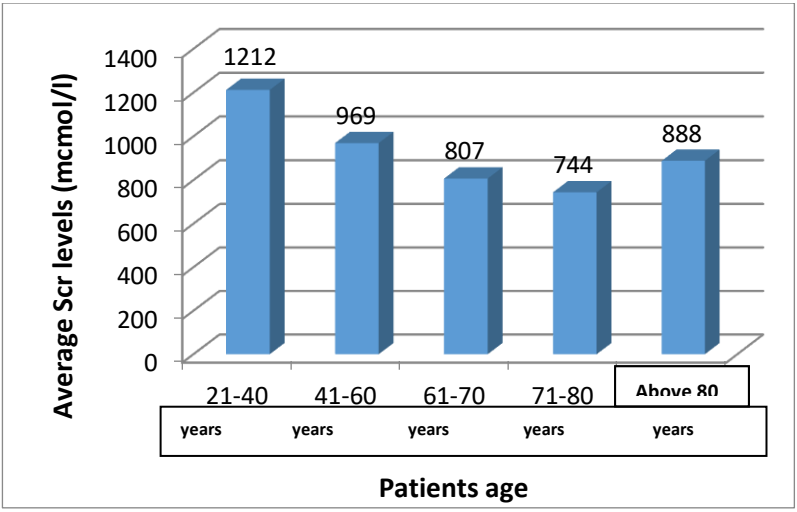

Figure №16. Average value of serum creatinine by the beginning of HDT in patients at different age (n=204).

The average level of serum creatinine at the beginning of HDT is credibly higher (p<0,001) in patients at age under 60 years, compared to patients at age from 61 to 80 years (fig. №6).

4.2.5. Comparison between patients who have and have not undergone treatment with ESA before hemodialysis initiation.

At the beginning of HDT 75/204 patients (36,8%) were treated with ESA in the predialysis period. The difference between the average hemoglobin levels in both groups of patients is credible. The average value of hemoglobin in patients who have undergone anemia treatment with ESA is below the lower border of the target interval about anemia correction (110-120 g/l).

Table №31. Comparison between the average values of hemoglobin and dose of ESA at the beginning of HDT and duration of HDT in patients with treated and untreated anemia before its initiation (n=204).

	Nr. patients	Hemoglobin (g/L)	Weekly Epo dose (UI)	Duration of HDT (mon.)
Treated with ESA before HDT start	75	99,6±14,5	5649±2665	43,0±26,4
Untreated with ESA before HDT start	129	91,1±16,1	6651±2262	34,7±27,9
p	-	0,001	0,005	0,038

The difference between the average weekly doses of ESA in both groups is also credible and the dose of epoetin for patients with previous anemia treatment is respectively credibly lower. The duration of HDT is credibly higher in patients with previous anemia treatment which allows to accept that better hematological markers at the beginning of HDT define a better survival rate (tabl. №31).

4.2.6. Analysis of the treatment of renal anemia in patients on hemodialysis treatment in time.

Results of our study show that at the beginning of HDT in 4/204 patients did not require treatment of anemia. The relative variable of untreated with ESA hemodialysis patients gradually increases from 2% in the first 6-month period of HDT to 15% in the fourth six-month period. For different periods of time the longest total duration of this marker fluctuates between 11 and 15%, and in the period 43-54 months even increases 20%. In patients with the longest duration of HDT – over 72 months the relative variable again increases 20% (tabl. №34).

Table №34. Comparison between the duration of HDT and number of patients, who do not need treatment of RA with ESA.

Period of HDT (mon.)	Nr. patients	Nr. patients untreated with Epo	Ref. var. (%)
0-6 mon.	204	4	2,0
7-12 mon.	196	12	6,1
13-18 mon.	168	17	10,1
19-24 mon.	153	23	15,0
25-30 mon.	129	16	12,4
31-36 mon.	107	12	11,2
37-42 mon.	95	14	14,7
43-48 mon.	78	17	21,8
49-54 mon.	64	14	21,9
55-60 mon.	51	7	13,7
61-66 mon.	43	5	11,6
67-72 mon.	35	5	14,3
Above 72 mon.	29	6	20,7

Distribution of patients treated with Epo alpha and Epo beta by number during the different six-month periods of the evaluation show unequal speed of decrease in their number in both groups. After the 24th month of treatment the number of patients treated with Epo beta becomes larger than the number of patients treated with Epo alpha. This difference gradually increases and in the last few periods of evaluation it is more than two times (tabl. №35). The dose of erythropoietin gradually decreases from 6335±2462 IU/weeky in the first six months to 3902±2152 IU/weekly in the eighth. Dose decrease is the highest in the second six-month period (average minus 531 IU) and at the third six-month period (average minus 725 IU). the therapeutic erythropoietin dose is the lowest during the tenth six-month period - 3727±2206 IU/weekly (tabl. №35). The differences between the average beginning epoetin dose and some of the average values for the six-month periods after the fourth are credible.

Table №35. Number of patients treated with both epoetin drugs and the total average therapeutic dose at the different six-month periods of the study.

Period of HDT (mon.)	Nr. patients, treated with Epo alpha	Nr. patients, treated with Epo beta	Epoetin dose (UI/weekly)
0-6 mon.	118	82	6335±2462
7-12 mon.	105	79	5804±2407
13-18 mon.	86	65	5079±2405
19-24 mon.	67	63	4892±2428
25-30 mon.	56	57	4137±2231
31-36 mon.	45	50	4063±2098
37-42 mon.	40	41	4185±2259
43-48 mon.	28	33	3902±2152
49-54 mon.	20	30	4120±2296

55-60 mon.	15	29	3727±2206
61-66 mon.	9	29	4566±2302
67-72 mon.	6	24	4517±2946
Above 72 mon.	4	19	4896±2574

The analysis of the therapeutic efficacy of the epoetin treatment shows that the hemoglobin level gradually increases from the beginning of the treatment up to the fourth six-month period when its average level is in the recommended therapeutic interval from 110 to 120 g/l (tabl. №36). The increase of the hemoglobin value is the highest in the first six-month period (average plus 9,4 g/l) and the second (average plus 4,6 g/l) biannual period. All in all, through 7/12 periods of supportive treatment (excluding first three periods, which are periods of anemia correction) the average hemoglobin level is in the frames of the target interval.

Table №36. Average values of hemoglobin, serum iron and transferrin saturation in the different periods of hemodialysis treatment.

Period of HDT (mon.)	**Hemoglobin (g/L)**	**Ser. iron (mcmol/L)**	**TSAT (%)**
0	94,1±16,1	10,7±5,9	26,4±12,0
6	103,5±12,5	11,2±4,6	26,4±9,5
12	108,1±13,6	11,1±4,7	25,8±9,1
18	109,1±14,2	11,6±4,9	26,3±9,3
24	112,0±12,4	12,2±4,8	28,1±8,7
30	111,1±11,0	12,2±5,9	27,1±9,4
36	110,6±12,6	12,2±5,2	28,8±9,2
42	113,4±14,2	11,8±5,4	26,4±8,9
48	111,5±13,9	12,8±6,7	29,5±12,0
54	110,6±11,7	12,1±7,1	26,8±11,1

60	111,3±13,5	13,6±7,8	30,3±12,2
66	109,1±15,8	12,2±5,9	26,4±8,9
Above 72	106,6±13,6	11,9±4,8	27,6±9,1

4.2.7. Analysis of the treatment of renal anemia and hemodialysis treatment in patients with different main diseases.

The distribution of patients at the beginning of hemodialysis treatment by main renal disease shows that the most common chronic nephropathies that lead to CKD and require organ substituting treatment are hypertensive nephropathy, diabetic nephropathy and chronic glomerulonephritis – total 148/204 or 72,5%.

ADPKD is located traditionally on fourth place after the other diseases (fig. №18).

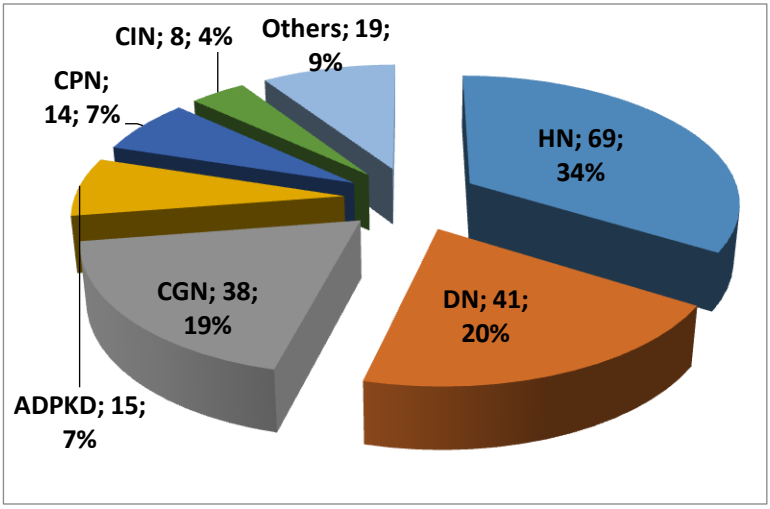

Figure №18. Distribution of patients at the beginning of HDT by main disease (n=204).

The average initial dose of erythropoietin is the highest in patients with ADPKD and CGN, the lowest in patients with HN and CPN/CIN (tabl. №38).

Table №38. Average values of epoetin doses and hemoglobin at the beginning of HDT in different disease groups.

Main disease	Dose Epo (UI/weekly)	Hgb (g/L)
ADPKD	6800±2833	95,5±14,1
CGN	6579±2627	89,2±194
DN	6427±2317	94,5±13,3
CPN+CIN	5905±2548	97,1±14,1
HN	5888±2369	96,1±16,4
Others	7389±2173	91,2±16,5

Hemoglobin is the highest in patients with interstitial nephritis, with HN and with ADPKD and the lowest in patients with chronic glomerulonephritis. The observed differences in the initial level of hemoglobin between patients with interstitial nephritis and CGN are at the border of statistical significance (p=0,052) and are bit significant for the other groups.

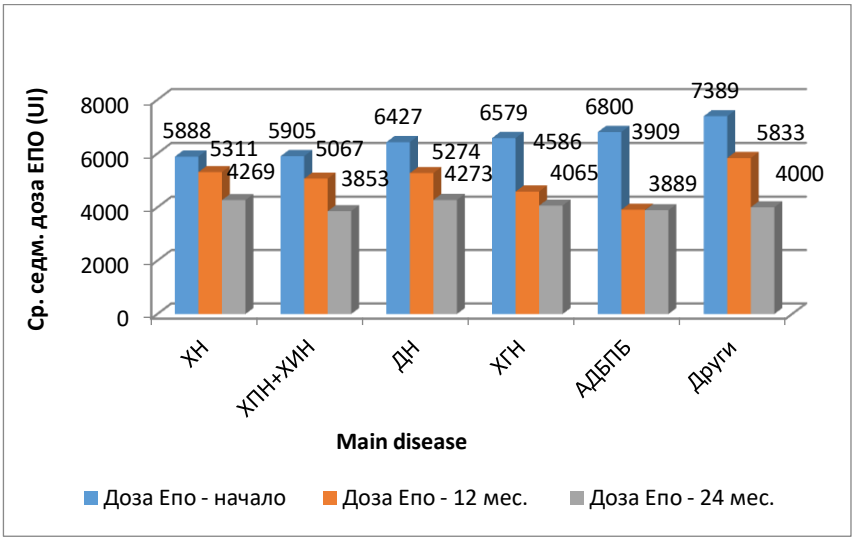

Figure №21. Average weekly epoetin doses in patients with different main disease during the first 24 months of hemodialysis treatment.

Initial epoetin weekly dose in patients with HN and CPN/CIN is below 6000 IU. Initial weekly epoetin dose in patients with DN, CGN and ADPKD is between 6400 and 6800 IU. The decrease of the weekly dose of epoetin after 12th month varies in the different groups from 577 IU (in HN) to 2891 IU (in ADPKD). The decrease in the weekly dose of epoetin after 24th month varies in the different groups from “insignificant” (in ADPKD) to 1833 IU (in “Others”) – fig. №21.

All dose changes are significant (p=0,001) and the practical lack of changes between the second and the third average dose (p=0,713) in patients with ADPKD shows that the exact supportive dose in these patients is reached up to the 12th month of HDT. The significance in the decrease in the average weekly doses is a good marker for effective correction of the renal anemia in all patients in the first several semiannual periods of HDT.

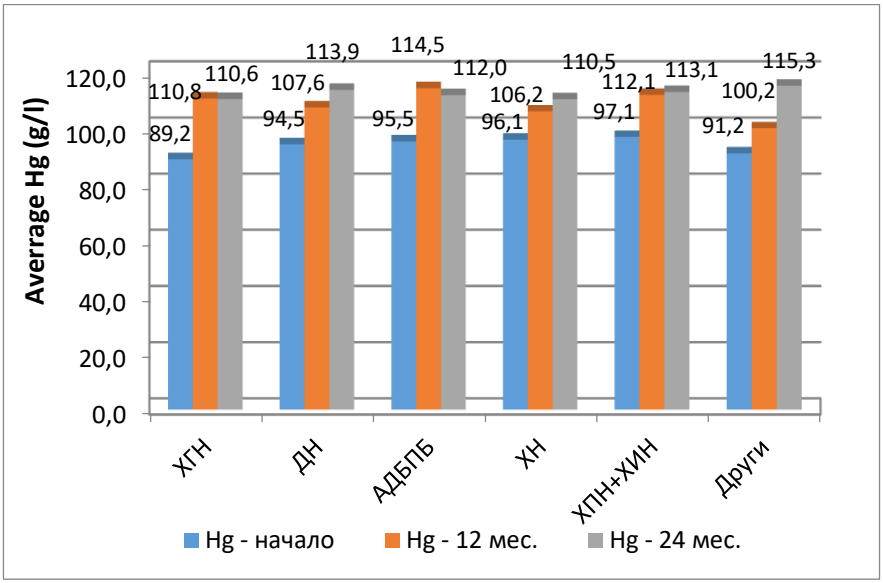

Figure №22. Average values of hemoglobin in different groups at the beginning, 12th month and 24th month of HDT.

The average values of hemoglobin at the beginning of HDT between the different groups vary in relatively narrow borders – from 89,2±19,4 g/l to 97,1±14,1 g/l. The average values at the 12th month vary from 110,5±11,7 g/l to 115,3±8,7 g/l. The average values of hemoglobin at the beginning of therapy and at the 12th month differ significantly for all groups of patients (p=0,001), whereas hemoglobin levels at 12th month and 24th month do not show significant differences (p=0,065). At the 12th month hemoglobin values were already in the target interval for three of the patient groups and in the other three hemoglobin was between 100,2±24,0 g/l and 107,6±10,6 g/l. At the 24th month all values were in the target interval (fig. №22).

4.2.8. Summary

1. Among patients who start HDT on CKD/CRF male patients are 14,8% more than female. The average age of all patients at the time

of HDR initiation is 62,6±13,1 years. Female patients are significantly older than male.

2. Duration of hemodialysis treatment in females (average 34,3±25,1 months) is insignificantly lower than in males (average 40,3±29,2 months). That is why we can conclude that at the beginning of HDT females are younger than males but the hemodialysis duration in them is lower.

3. The youngest patients (12-40 years) have more than two times higher average length of HDT – 48,5±29,7 months compared to the average length in the oldest (above 80 years) – 22,2±22,1 months. The difference in the duration of HDT between the different age groups are significant. Dependence between duration of HDT and age is linear and is described with the equation: Length of HDT (in months) = 73,61 - 0,268 x age.

4. In most patients – 40% at the initiation of HDT the value of serum hemoglobin was from 81 to 100 g/l. In 18,6% of patients, anemia was extremely severe with hemoglobin value below 80 g/l.

5. Contrary to the logical assumption, anemia is significantly more severe in the youngest and the lightest in patients at age between 71 and 80 years. Comparison between the average values of hemoglobin at the beginning of HDT and its duration shows that patients with more severe anemia have a greater survival rate than patients with lighter anemia. This brings the conclusion that the presence of anemia at the beginning of the organ substituting treatment is not the only factor that defines the treatment prognosis.

6. In most of the patients – 115/204 (56,3%), HDT began when the serum creatinine level was from 600 to 1000 mcmol/l. In more than ¼ of the patients the organ substituting treatment began at significantly higher levels of creatinine.

7. The average value of serum creatinine at the beginning of HDR is the highest in patients with the longest treatment duration. This brings us to the conclusion that the “belated” start of HDT, defined

by the initial level of serum creatinine is not the leading factor for reduced survival on this dialysis method.

8. The difference between the average levels of hemoglobin in patients treated with ESA before the initiation of HDT – 99,6±14,5 g/l and untreated patients – 91,1±16,1 g/l is credible. The difference between the initial average weekly doses of ESA in both groups, respectively 6651±2262 IU and 5649±2665 IU is also credible.

9. The duration of HDT is significantly higher in patients with previous anemia treatment, which allows us to accept that better hematological markers at the beginning of HDT especially in this group of patients, define better survival rate.

10. Patients with previous treatment of renal anemia at the beginning of HDT have significantly better RF compared to patients without previous treatment of anemia. All differences are enough to confirm the necessity of treatment of the RA in the predialysis stage for all patients with CKD.

11. With the increase in the duration of HDT, the relative variable of patients, in whom decreased application of ESA is not necessary (up to 15-20% for different periods of evaluation), gradually increases. This marker serves as an excellent indicator for high quality of HDT and of renal anemia.

12. The average initial dose of Epo beta at the beginning of HDT is significantly higher than the initial dose of Epo alpha. The average erythropoietin dose gradually decreases from the first semiannual period to the eight six-month period. Some of the differences are significant.

13. The average value of hemoglobin increases gradually from the beginning of the treatment to the fourth six-month period, when it reaches the recommended therapeutic target from 110 to 120 g/l. Because of the more severe renal dysfunction and the specific character of the HDT, anemia correction during the period of this treatment happens slower compared to the predialysis period.

14. The most common chronic nephropathies that lead to CKD and require organ substitution treatment are hypertensive nephropathy, diabetic nephropathy and chronic glomerulonephritis. The duration of hemodialysis treatment is the largest in patients with autosomal dominant polycystic kidney disease and chronic pyelonephritis/chronic interstitial nephritis.

15. The average weekly dose of erythropoietin is the highest in patients with autosomal dominant polycystic kidney disease and chronic glomerulonephritis, and the lowest in patients with hypertensive nephropathy. There is no correlation found between the lowering of the erythropoietin dose and the elevation of hemoglobin in the time of HDT and the main renal disease.

4.3. TREATMENT OF RENAL ANEMIA WITH ESAs IN PATIENTS WITH CKD UNDERGOING TREATMENT WITH PERITONEAL DIALYSIS.

4.3.1. Social and demographical characteristics of the evaluated group.

The study is conducted with 51 patients with CKD stage 5, in whom treatment with peritoneal dialysis was begun and performed for the period 2012-2021.

Female patients are 25 at average age at the beginning of renal replacement therapy 52,0±15,5 years, and males are 26 – at average age at the beginning of renal replacement therapy 56,2±14,3 years. the total average age is 54,2±15,0 years.

Duration of treatment with PD varies from 5 to 121 months – average duration is 31,7±25,3 months. The average duration of treatment in females is significantly higher than in males ($p<0,043$) (tabl. №39).

Table №39. Distribution of patients by gender, average age and duration of treatment with peritoneal dialysis.

	Number	Average age (years)	Duration of treatment with PD (mon.)
Female	25	52,0±15,5	38,4±32,3
Male	26	56,2±14,3	25,3±22,9
Total	51	54,2±15,0	31,7±25,3

4.3.2. Analysis of the treatment of RA with different ESAs at the beginning of treatment with PD.

Treatment of RA with epoetin is initiated immediately after the beginning of treatment with peritoneal dialysis in 48/51 patients. This treatment was performed with two rapid-acting recombinant epoetin agents – Epoetin alfa and Epoetin beta.

The dose of epoetin before the initiation of the treatment with peritoneal dialysis varies from 1500 to 9000 IU/weekly. Data analysis regarding the dose of each of the two drugs in patients from both genders shows equal, completely comparable values in females, treated with both drugs. Significantly higher is the average dose of Epo alpha in males compared with the same dose in females. The difference between the average dose of Epo alpha and dose of Epo beta in all patients is insignificant (tabl. №42).

Table №42. Average initial doses of Epo alpha and Epo beta in patients from both genders (n=51).

	Epo alpha (UI/weekly)	Epo beta (UI/weekly)	p	Total (UI/weekly)
Female	5500±2746	5647±2517	0,884	5609±2402
Male	6900±2025	5600±2746	0,038	6120±2471
Total	6375±2156	5625±2584	0,115	5875±2453

4.3.3. Severity of anemia at the beginning of peritoneal dialysis treatment.

At the beginning of the treatment with peritoneal dialysis the level of hemoglobin varies from 49 to 125 g/l. In 33,4% of patients anemia was very severe with hemoglobin value below 90 g/l. Less than one fourth of the patients were with hemoglobin value above 110 g/l. (tabl. №43).

Table №43. Distribution of patients at the beginning of treatment with PD based on hemoglobin value (n=51).

Hemoglobin (g/L)	Nr. patients	Ref. var.
Below 70	3	5,9%
71-90	14	27,5%
91-110	22	43,1%
Above 110	12	23,5%
Total	51	100,0%

4.3.4. Analysis of the treatment of RA in time.

The effectiveness of treatment of RA and simultaneously the effectiveness of PD can be better evaluated with the number of patients who did not require application of epoetin in the different follow-up periods as well. The relative variable of patients who had optimal target levels of hemoglobin without epoetin application increases rapidly after the 24th month of treatment with PD and is in levels between 35 and 40% until the 54th month. The relative variable of untreated with epoetin after the 54th month is ignored because of the small number of the evaluated patients (tabl. №46).

Table №46. Number of patients who underwent treatment with epoetin and patients who did not undergo such treatment in the different periods of treatment with PD.

Period of treatment with PD (mon.)	Total Nr. patients treated with PD	Nr. patients untreated with Epo	Ref. var. of untreated with Epo (%)
0-6	51	3	**5,9%**
7-12	51	5	**9,8%**
13-18	46	5	**10,9%**
19-24	36	14	**38,9%**
25-30	30	12	**40,0%**
31-36	24	9	**37,5%**
37-42	16	6	**37,5%**
43-48	14	5	**35,7%**
49-54	11	4	**36,4%**
55-124	6	5	-
61-124	3	2	-
103-121	2	1	-

The effectiveness of antianemic treatment can be evaluated not only with the reduction of patients treated with epoetin in time but also with the gradual reduction of epoetin doses. The average epoetin dose at the beginning of treatment with PD and RA is 5875±2453 UI/weekly. The dose gradually and progressively decreases until the 48th month of treatment with PD, when it reaches 2056±982 UI/weekly. This way epoetin dose is reduced almost three times compared to the initial. The differences between the average epoetin doses for the first nine six-month periods are significant – $p<0,001$ (fig. №25).

Figure №25. Average values of epoetin doses in the different peritoneal dialysis treatment periods.

Table №47. Average values of hemoglobin, serum iron and transferrin saturation in different periods of treatment.

Period of treatment with PD (mon.)	Hemoglobin (g/l)	Ser. iron (mcmol/L)	TSAT (%)
0	100,0±16,1	10,6±5,8	24,1±10,6
6	110,2±8,6	12,6±4,6	27,6±7,7
12	114,4±10,1	12,8±5,1	28,5±9,1
18	120,6±10,7	12,7±4,2	27,8±7,5
24	121,2±9,3	12,7±3,9	27,8±8,3
30	120,8±10,4	11,6±4,0	25,8±7,0
36	122,6±10,9	14,0±3,8	29,4±5,5
42	124,1±13,1	12,4±3,5	26,9±5,9
48	123,5±9,0	15,4±3,0	30,7±5,5
54	133,2±5,9	13,3±4,3	28,2±7,0
60-102	127,8±8,6	12,2±3,6	23,3±5,3
108-121	122,5±22,5	12,3±3,7	23,2±6,0

Analysis of the levels of hemoglobin in different six-month periods of evaluation shows rapid increase through the first 18 months, confirmed by the significant difference (p=0,001) and maintenance in levels above 120 g/l after that and until the end of the treatment with PD (p=0,854). The average valurs of serum iron and transferrin saturation are in optimal levels and show that substituting therapy with oral and parenteral application of iron-containing drugs is performed “lege artis” (tabl. №47).

4.3.6. Summary

1. Anemia in patients with CKD treated with PD has equal, comparable severity in all age groups.

2. There is no connection between the severity of anemia and duration of CKD treatment with PD.

3. The correction of anemia is effective in all patients and in part of them epoetin treatment is terminated for different periods of time.

The relative variable of patients who did not require RA treatment with epoetin gradually increases from 5,9% at the beginning to levels between 35 and 40% up to the 54th month of the study.

4. The dose of epoetin progressively decreases from 6th to 48th month of treatment with PD from 5875±2453 to 2056±982 UI/weekly. That way epoetin dose is reduced almost three times, compared to the initial. The differences between the average epoetin doses for the first nine six-month periods are significant.

5. Hemoglobin values rapidly increase in the first three six-month periods of treatment, where the differences are significant and remain stable after that in levels up to and above 120 g/l until the end of treatment.

6. The average values of creatinine and urea in all six-month periods after the first are in the frames of second stage CRF and show that RRT with PD is performed effectively, which is one of the main requirements for effective and cheaper treatment of RA.

4.4. COMPARISON BETWEEN THE TREATMENT OF RENAL ANEMIA WITH ESA IN PATIENTS WITH CKD TREATED WITH HEMODIALYSIS AND PERITONEAL DIALYSIS.

4.4.1. Comparative analysis of treated groups, anemia parameters, renal function and doses of ESA.

The duration of hemodialysis treatment until its termination or until the time of the study varies from 6 to 114 months and is averagely 37,7±27,7 months. The duration of PD treatment varies from 5 to 121 months – average duration is 31,7±25,3 months. The difference from 6 months between the average duration of treatment with both dialysis methods is not significant – p=0,161.

Comparison between the age of patients, treated with HD and PD shows that the average age of the first is 62,6±12,9 years is significantly higher than the average age of the second – 54,2±15,0 years (p<0,001).

The average hemoglobin value at the time of initiation of treatment with HD was 94,1±16,1 g/l, at PD initiation – 100,0±16,1 g/l, the difference is significant – p=0,02.

Generally more patients who begin treatment with PD have lighter anemia, compared to patients who begin treatment with HD or overall – anemia in patients who begin treatment with PD is significantly lighter, than anemia in patients who begin HD treatment.

Comparison between epoetin doses in different periods of dialysis treatment shows that for the whole period of treatment the average doses in patients treated with PD were lower compared to doses in patients treated with HD. The differences for most periods are significant (tabl. №49), (fig. №27).

Table №49. Average values of doses of epoetin during the different dialysis treatment periods.

Duration of dialysis treatment (mon.)	Nr. patients treated with HD and Epo	HDT – epoetin dose (UI/weekly)	Nr. patients treated with PD and Epo	Treatment with PD – epoetin dose (UI/weekly)	p
0-6 mon.	200	6335±2462	48	5875±2453	0,246
7-12 mon.	184	5804±2407	46	4761±1968	0,007
13-18 mon.	151	5079±2405	41	3573±1856	0,001
19-24 mon.	130	4892±2428	22	3159±1515	0,001
25-30 mon.	113	4137±2231	18	3000±1618	0,004
31-36 mon.	95	4063±2098	15	2500±1323	0,007
37-42 mon.	81	4185±2259	10	2150±973	0,006
43-48 mon.	61	3902±2152	9	2056±982	0,014
49-54 mon.	50	4120±2296	7	2429±976	-
55-60 mon.	44	3727±2206	1	3000±1000	-
Above 60 mon.	38	4709±2561	1	1357±864	-

Analysis of hemoglobin value in different periods of both methods of dialysis treatment shows that the average values are always higher in patients treated with PD (tabl. №28). For some of the periods the differences are significant. This is the primary reason epoetin doses in this method of RRT to be lower.

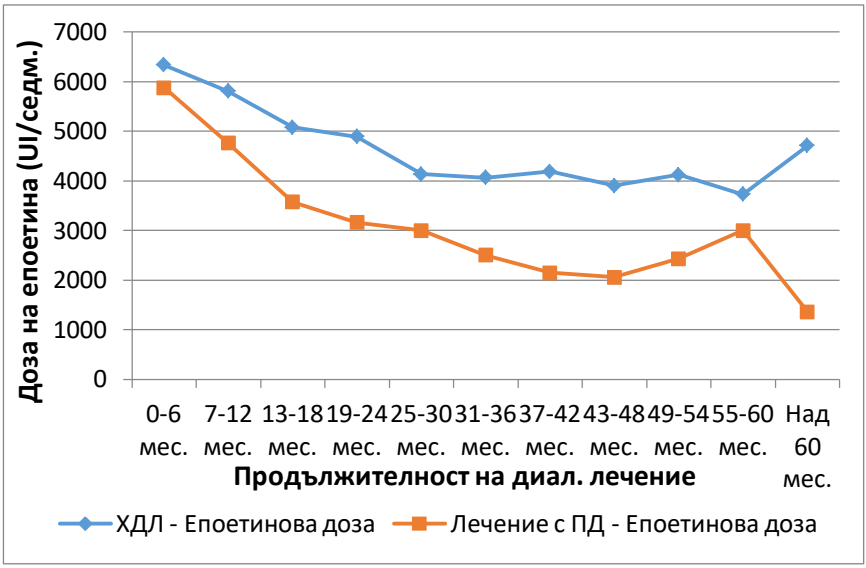

Figure №27. Average values of doses of epoetin during the different dialysis treatment periods.

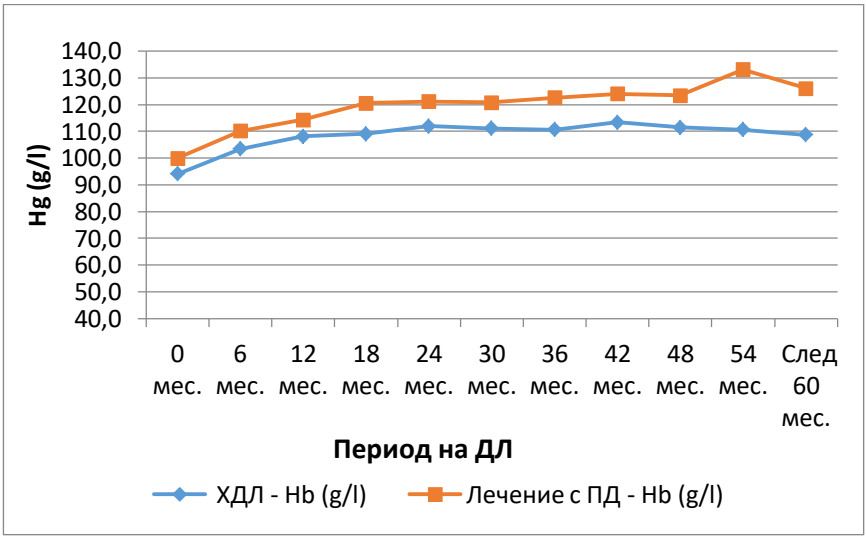

Figure №28. Average values of hemoglobin in different periods of dialysis treatment.

4.4.2. Conclusion

1. At the time of initiation of RRT, patients treated with HD are older than those, treated with PD. Despite that, the average duration of hemodialysis treatment of CKD is significantly higher than the average duration of PD treatment.

2. Anemia in patients who begin treatment with PD is significantly lighter than anemia in patients who begin treatment with HD. Correction of anemia, evaluated by hemoglobin levels, with ESA is significantly better in patients treated with PD.

3. ESA doses in patients treated with PD are lower than doses in patients treated with HD. This way treatment of RA in patients on PD is performed with lower doses of recombinant erythropoietins, which defines lower financial costs.

4.5. QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE.

4.5.1. Quality of life in patients with chronic kidney disease in predialysis stage.

4.5.1.1. Characteristics of evaluated group based on demographical markers, anemia and renal dysfunction.

The evaluated group includes 60 patients with CHD stage I-IV in predialysis stage, who undergo treatment with one and the same epoetin drug – Epo alpha.

Patients' age varies from 60 to 87 years, average – 72,5±7,2 years. Females are 38 (63,3%), their average age is 71,8±7,1 years, and males are 22 (33,7%), at mean age - 73,8±7,4 years. Most patients are from the cities population, more than two thirds (83,3%) have finished high school or university, 66,7% are married. The current study finds that only 18,3% do regular follow ups.

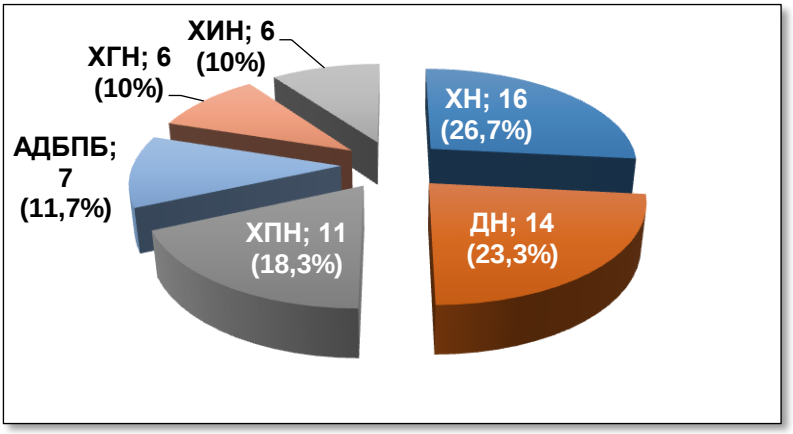

Figure №29. Etiology of CKD in predialysis (n=60).

The most common main renal diseases are HN and DN, and the rarest – CGN and CIN (fig. №29).

The analysis of laboratory markers at the beginning of renal anemia treatment in patients from both genders finds completely comparable levels of haemoglobin, red blood cells, serum creatinine, urea and glomerular filtration. (tabl. №52). In all patients at the first stage, as well as after six months, no hypoproteinemia or hypoalbuminemia have been registered.

Table №52. Laboratory markers in males and females before initiation of treatment with Epoetin alpha.

	Age	Hg (g/l)	Hct	RBC ($.10^{12}$/l)	Scr (μmol/l)	Urea (mmol/l)	CrCl (ml/min/ 1,72m2)
Female	71,8±7,1	100,9±8,2	0,29±0,04	3,2±0,3	282±116	21,8±5,2	20,9±10,3
Male	73,8±7,4	104,3±3,9	0,31±0,03	3,5±0,4	296±105	22,4±5,8	20,4±10,3

There are no significant differences in the values of these markers in the groups with different main renal diseases.

Analysis of the value of ths score before initiation of treatment with RA with epoetin in the common panel shows lower score in the domains for body pain (BP), general health perception (GHP), social function (SF) and vitality (VEF). All average values in these domains are under 50 (tabl. №54).

In the organ specific domain before initiation of anemia treatment the lowest score is in evaluation of sexual function (SXF), quality of social life (QSI), severity of CKD (BKD) and sleep (SLP) (tabl. №55). Overall the score in social domains in lower than the score in organ specific.

After 6-month treatment of renal anemia with epoetin an increase in the score in all domains is registered, both common (tabl. №54), and organ specific (tabl. №55).

An exception make the values of support from the medical personnel (DSE) and patient satisfaction from treatment (PST), which have maximal score from the first test.

Table №54. Evaluation of the change of QL after 6-month treatment of RA – common domains.

	FF	RL	BP	GHP	EWB	RLE	SF	VEF
Beginning	55,6± 14,8	56,6± 16,6	46,5± 18,1	48,0± 5,2	50,8± 12,2	75,2± 21,9	49,4± 11,5	45,0± 8,4
Post 6 months	82,6± 8,5	82,3± 16,7	78,1± 14,8	69,4± 10,1	70,9± 12,4	95,8± 8,9	61,3± 11,9	70,4± 11,8
Average difference	27,0	25,7	31,6	21,4	20,1	20,7	12,0	25,4
Change (in %)	+32,7%	+31,2%	+40,2%	+30,8%	+28,4%	+21,6%	+19,5%	+36,1%
p	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001

Evaluation of the change in QL after 6-month treatment and correction of anemia shows that the larger increase that illustrated increase in QL is present in the score of domains in the common panel, compared to the organ specific panel. An absolute increase in the common paannel varies from 12 to 27 puncts, and variable – from 19,5 to 40%. All diffrences are significant. (tabl. №54).

Table №55. Evaluation of the change in QL after 6-month treatment of RA – organ specific domains.

	SL	EFKD	BKD	WS	CGF	QSI	SXF	SLP	SS
Beginning	65,5 ±10,1	69,7 ±15,7	52,4 ±8,7	64,2± 22,7	60,5 ±9,5	51,4 ±8,5	49,0 ±24,6	54,3 ±7,8	63,4 ±14,9
Post 6 months	87,0 ±5,9	91,1 ±8,7	82,0 ±14,5	73,5± 22,5	82,9 ±9,1	74,1 ±7,5	58,1 ±26,9	76,6 ±8,0	82,4 ±17,4
Average difference	21,5	21,4	29,6	9,3	22,4	22,8	9,2	22,3	19,0
Change (in %)	24,7%	23,5%	36,1%	12,7%	27,0%	30,7%	15,8%	29,1%	23,0%
P	<0,001	<0,001	<0,001	>0,05	<0,001	<0,001	<0,001	<0,001	<0,001

Evaluation of the change in QL, evaluated with the organ specific panel, shows that absolute increase in score varies from 9,2 to 29,6 puncts, and variable increase – from 12,7% to 36,1%. After 6-month treatment of RA improvement of QL related to sexual function (SXF)

is the lowest (average score 58,1, increase with 9,2). The differences between the score at initiation and post 6 months is significant for all domains, excluding the domain for working status (WS) (tabl. №55).

4.5.1.3. Evaluation of quality of life in patients with CKD in predialtsis stage – comparison between both genders.

Before RA treatment initiation in females lower score in 8/19 domains, whereas in males in 6/19 domains. In the other 5/19 domains self-assessment is equal. Patients from both genders assess equally the QL, related to BP (body pain), EWB (emotional well-being), QSI (quality of social life), DSE (support from the medical staff), PST (satisfaction of patient) (tabl. №56 and №57).

The highest score is marked from both genders in the domains for satisfaction of the patient (PST) and support from medical staff/nephrologist (DSE). Low score is registered in both genders related to quality of life, connected to body pain (BP), emotional well-being (EWB) and vitality (VEF).

Differences in self-assessment of QL between both genders is registered in a total of 14 domains, but the differences are significant only in 7 of them (tabl. №56 and №57). We can assume that the grouped and commented domains are highly connected to the psycho-social differences between male and female in general. All in all, the comparison shows higher quality of life in females with CKD before initiation of treatment of RA.

Table №56. Evaluation of QL in patients from both genders before initiation of treatment of RA – markers in the common domains (n=60).

	FF	RL	BP	GHP	EWB	RLE	SF	VEF
Female	59,4 ±13,7	54,6 ±17,5	47,3 ±17,6	46,8 ±4,9	50,8 ±12,5	79,9 ±21,8	47,6 ±11,8	43,3 ±6,1
Male	49,2 ±14,7	60,2 ±14,7	45,3 ±19,4	50,0 ±5,4	50,9 ±11,8	67,1 ±20,0	52,5 ±10,7	48,0 ±10,9

p	**<0,02**	>0,05	>0,05	**<0,05**	>0,1	**<0,05**	>0,05	>0,05

Table №57. Evaluation of QL in patients from both genders before initiation of treatment of RA – values for organ specific domains (n=60).

	SL	**EFKD**	**BKD**	**WS**	**CGF**	**QSI**	**SXF**	**SLP**	**SS**
Female	66,7 ±11,1	76,1 ±13,5	53,9 ±9,5	66,7 ±23,9	59,4 ±9,6	51,8 ±7,7	43,5 ±27,0	52,4 ±6,1	61,1 ±14,0
Male	63,4 ±10,6	57,8 ±12,3	49,7 ±6,4	59,6 ±20,1	62,5 ±9,4	50,6 ±10,0	53,6 ±22,2	57,9 ±9,4	68,6 ±16,0
p	>0,1	**<0,001**	**<0,05**	>0,05	**<0,05**	>0,1	>0,05	**<0,05**	>0,05

After 6-month treatment of RA with epoetin we found differet increase in the score that evaluates QL in patients from both genders in all domains from both panels with the exception of support from medical personnel (DSE) and patient satisfaction (PST), which are with a maximum score, just like before treatment initiation. In some domains this score elevation is significant. In females only in one of the domains the score is below 60, in 12/19 domains the score is above 70. In males the score is below 60 in one domain, and in 14/19 domains it is above 70. In 14/17 domains the score is higher in males. The difference between the score in males and females is significant only in five domains. We also found that after 6-month treatment of anemia the score is even lower in females in 14/16 domains, and in males only in 2/16. This way the improvement of the QL is significant in patients from both genders, but in males this improvement is greater than in females (tabl. №58 and №59).

Table №58. Evaluation of QL in patients from both genders after 6-months treatment of RA – values in the common domains (n=60).

	FF	RL	BP	GHP	EWB	RLE	SF	VEF
Female	82,4± 5,3	79,0± 17,5	77,6± 13,4	67,7± 9,6	69,5± 12,0	94,8± 10,2	59,0± 11,4	68,3± 9,8
Male	83,0± 12,4	88,0± 14,0	79,0± 17,2	72,2± 10,6	73,3± 12,9	97,6± 5,5	65,4± 12,0	74,0± 14,2
p	>0,1	**<0,05**	>0,1	>0,1	>0,1	>0,1	**<0,05**	>0,1

Table №59. Evaluation of QL in patients from both genders after 6-month treatment of RA – values for the organ specific domains (n=60).

	SL	EFKD	BKD	WS	CGF	QSI	SXF	SLP	SS
Female	86,2 ±5,2	91,1± 7,6	78,7± 13,9	78,2± 22,1	81,9 ±9,2	72,8± 4,1	68± 14,4	75,6± 7,6	78,9± 16,8
Male	88,3 ±6,5	90,1± 10,5	87,8± 13,9	65,4± 21,4	84,7 ±8,7	76,4± 11,0	43,8± 31,5	78,4± 8,5	88,4± 16,9
p	>0,1	>0,1	**<0,02**	**<0,05**	>0,1	>0,1	**<0,01**	>0,1	>0,05

In females QL improvement after 6-month treatment of RA with epoetin in part of the domains is above 40%. The average elevation of the score is from 11,0 to 30,2 puncts or from 23,0 to 63,6% (fig №30).

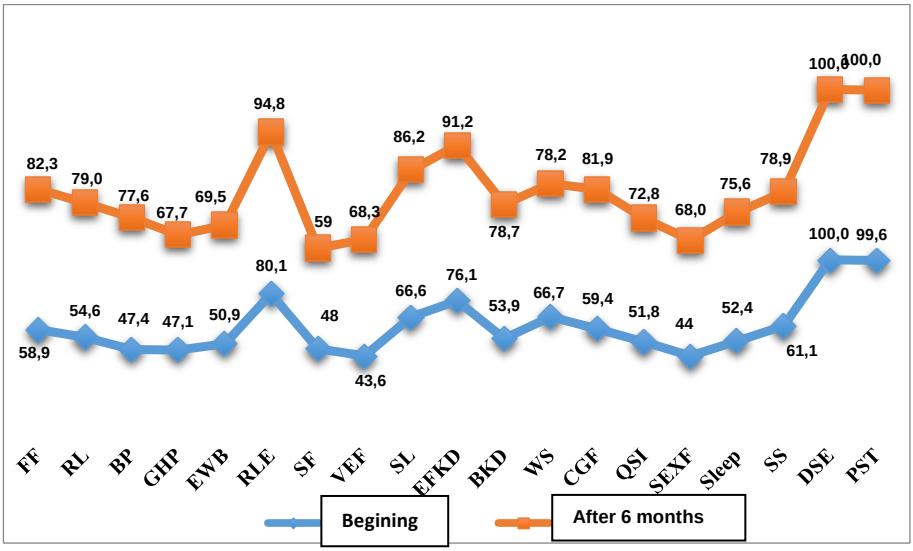

Figure №30. Comparison of the values of QL in females before and after 6-month treatment of anemia – all domains (n=38).

In male patients after 6-month treatment of anemia an improvement of QL is registered in all domains except for the one for evaluation of sexual function, in which a downgrade is registered. An important reason for this is the refusal of most males during the re-test to respond to the questions regarding sexual function. This makes the result to be registered, but to be drawn out and commented in the comparisons. An increase in the score at the sixth month with 40-50% is registered in males in four domains, with 51 to 60% - in three and above 60% - in three domains. The smallest improvement of QL is in the domain that presents the working status (WS), probably because of the fact that most of the evaluated males are in pension age. The average increase of the score in males varies from 5,9 to 38,1 punts or from 9,9 to 76,7% (fig. №31).

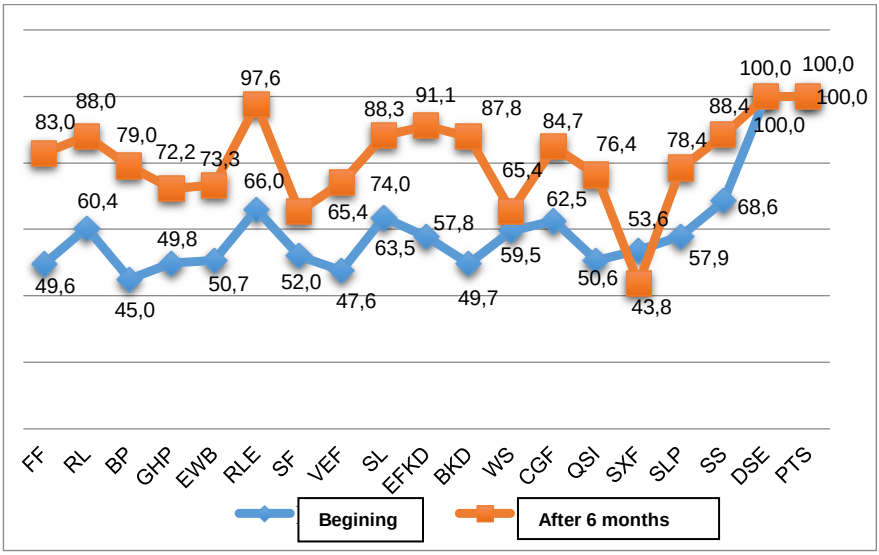

Figure №31. Comparison between the evaluation of QL in males before and after 6-month treatment of anemia – all domains (n=22).

The improvement of the QL is connected primarily with RA connection. In males we found that the hemoglobin increase with the average of 11,2 g/l (10,7%), of the number of red blood cells and hematocrit - with around 16%. Simulataneously with that we registerted a decrease in the serum creatinine and urea – respectively with 31% and 32%. The decrease in the serum creatinine is on the average with 86 mcmol/l, and the eGFR has increased with more than 50%.

In females the results from the conducted erythropoietin treatment are better. The hemoglobin increase is with 14,4 g/l, hematocrit and red blood cell count have increased with over 20%. The residual renal function has improved – serum creatinine has reduced averagely with 84 mcmol/l, urea with 5 mmol/l and eGRF has increased with average 9,7 ml/min/1,72m2, which is 54%.

4.5.2. Quality of life in patients with chronic kidney disease on dialysis treatment.

4.5.2.1. Social and demographical characteristics of the evaluated group.

The QL research includes 84 patients with CKD stage 5, who undergo RRT: 70 on hemodialysis treatment, 14 on treatment with peritoneal dialysis. These patients are at the age between 21 and 84 years, average age is 56,3±15,6 years, average duration of renal replacement therapy is 63,7±68,2 months. Females are 42, males are also 42. The average age of the female patients is 54,3±14,4 years, average dialysis treatment duration is 59,1±57,7 months. In male patients the average age is 57,8±13,8 years, average dialysis treatment duration at the time of the study is 68,3±77,7 months. The patients with CKD/CRF duration between 5 and 10 years are the highest number – 47,6%. The villagers are predominant (66,7%), those who have university and higher education are more than 50%. Most of the studied patients are married (53,6%).

4.5.2.2. Evaluation of the quality of life in patients with CKD treated with dialysis.

The evaluation of QL shows the highest results in the domains for patient satisfaction (PST) and support from medical personnel (DSE). High results are measured in the domains – body pain (BP), symptoms (SL), effect of kidney disease on the life (EFKD), cognitive function (CGF), sleep (SL) – the score in all of them is over 70%. In most domains – 9/19 the score is between 50 and 60. In the whole group of patients in dialysis treatment there is no domain with a score below 50, there are no domains with worryingly low scores and respectively – very poor QL (fig. №32 and №33).

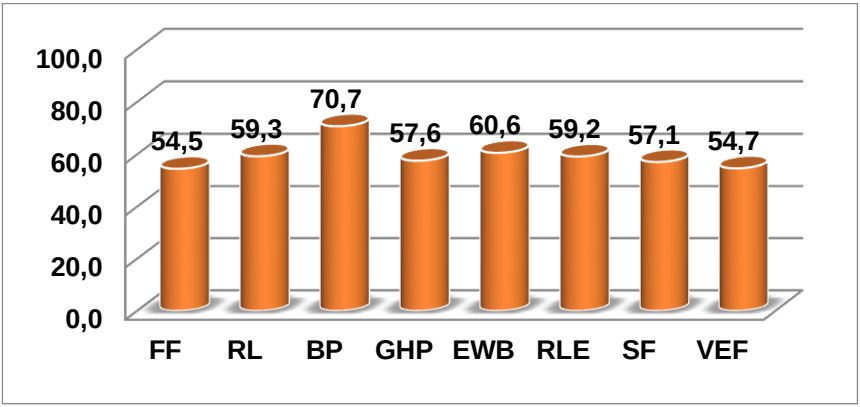

Figure №32. Quality of life in patients on dialysis treatment – common domains (n=84).

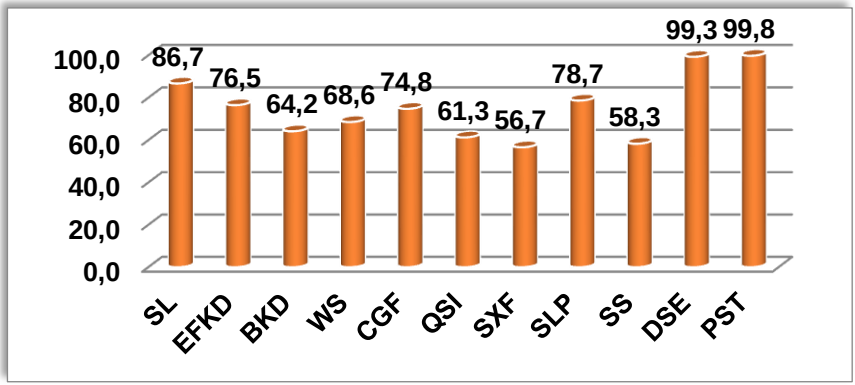

Figure №33. Quality of life in patients on dialysis treatment – organ specific domains (n=84).

4.5.2.3. Quality of life in patients with CKD on treatment with dialysis – comparison by gender.

In all domains – in males and females the average QL score is above 50. In females the score is above 70 in 7/19 domains. In males the score is above 70 in 6/19 domains. In 12/19 domains the difference between the scores in males and females is practically

equal – the differences are less than 2 puncts. Overall this way – lesser and greater differences between the average values of the scores of QL in patients from both genders are not significant (p>0,1) (fig. №34).

In the target domains, connected to CKD/CRF and dialysis treatment, excluding the domain for sexual function, a score from 60 to 100 is registered for both genders. The domain for sexual function cannot be properly compared with the other domains, because part of the males, who undergo hemodialysis treatment refused to answer the questions from this domain.

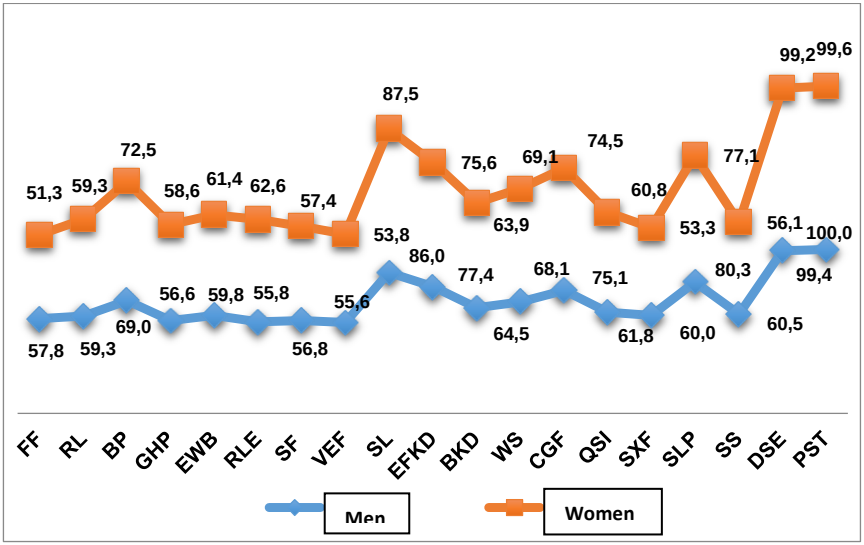

Figure №34. Evaluation of QL (score) in patients undergoing dialysis treatment from both genders in all domains (n=84).

Analysis of the date for QL, distribute by age groups, the highest score is registered in all domains in the youngest patients. In the panel for common domains the lowest are the scores of QL in the oldest.

Table №69. Evaluation of the quality of life in patients, treated with dialysis based on age – common domains (n=84).

Age	FF	RL	BP	GHP	EWB	RLE	SF	VEF
21-49 y.	68,6± 21,6	72,7± 24,9	78,6± 18,2	61,9± 9,3	61,3± 14,1	62,1± 27,5	65,1± 17,7	61,5± 12,0
50-59 y.	53,3± 23,2	54,1± 24,4	71,9± 21,5	55,0± 9,8	60,8± 12,6	54,0± 23,2	55,3± 20,9	51,5± 16,7
60-70 y.	53,6± 24,7	59,4± 24,2	67,4± 17,6	57,5± 14,2	61,1± 13,6	65,5± 27,4	55,7± 22,3	55,3± 16,0
71-84 y.	28,7± 23,0	38,1± 25,5	59,8± 23,7	52,3± 15,1	57,9± 15,9	47,0± 17,8	45,8± 26,3	43,5± 19,6

Table №70. Evaluation of the QL in patients treated with dialysis by age – organspecific domains (n=84).

Age	SL	EFKD	BKD	WS	CGF	QSI	SXF	SLP	SS
21-49 y.	89,0± 9,6	81,9± 11,3	67,7± 15,5	78,7± 28,3	77,7± 12,7	61,6± 8,5	Н. д.	78,1± 13,8	61,9± 22,2
50-59 y.	82,6± 12,1	75,9± 12,1	57,2± 16,7	69,1± 42,9	69,5± 15,3	59,2± 15,3	Н. д.	76,8± 12,0	58,4± 26,7
60-70 y.	85,8± 11,9	75,1± 14,6	65,3± 20,4	65,2± 38,2	74,1± 16,7	62,0± 9,9	Н. д.	79,7± 12,4	58,3± 24,5
71-84 y.	89,3± 7,1	68,9± 15,7	63,9± 19,8	53,8± 38,0	77,1± 14,3	62,0± 12,3	Н. д.	80,5± 11,1	50,8± 25,6

Overall in the panel for the organ specific domains the scores in all age groups are higher than in the panel of the common domains (tabl. №69 and №70). The last can be connected to the good patient adaptation to the chronic dialysis treatment, for which a big contribution has the work of the personnel of the dialysis unit, scored by all patients in the domains “patient satisfaction” and “support from the dialysis staff”.

4.5.3. Conclusion

1. Before the beginning of the treatment of RA in the predialysis period the worst QL is reported in half of the common and organ specific domains, which evaluate primarily the scores for health, social function, quality of social life, vitality, sleep and in a lesser stage evaluate the CKD.

2. After 6-month treatment of RA with epoetin in predialysis it is found that there is an increase in the score for QL in all domains, which varies from 12,7 to 40,2%. The highest is the improvement in the domains “vitality” and “body pain”, and is the lowest in the domain for sexual function.

3. Before the initiation of the treatment of RA in predialysis QL is comparable in patients from both genders. After 6-month treatment of anemia the improvement of QL is better in males.

4. After 6-month treatment of renal anemia with epoetin is predialysis, the correction is optimal. This shows the registered improvement in both the renal function and the QL.

5. In patients who undergo dialysis treatment a high score in QL is registered in the domains connected directly with the illness – in all of them the score is above 70. In the whole group of patients who undergo dialysis treatment there is no domain with a score below 50 and there are no domains that indicate a very poor quality of life.

6. In patients from both genders, who undergo dialysis treatment for CKD, QL is equal. In 12/19 domains the scores in females and males are completely comparable – all differences are less than 2 puncts. The differences in all domains are insignificant.

7. All patients with CKD/CRF – in predialysis and who undergo dialysis treatment score continuously in all time intervals and equally high QL in two domains – “Support from the medical staff” and “Satisfaction from treatment”. Larger part of the patients, who undergo hemodialysis treatment, primarily males, refuse to evaluate QL in the domain for sexual function.

5. Conclusions

1. Supports the connection between RF and anemia in patients with CKD in predialysis. The study found a continuous, lineary decrease in the average level of hemoglobin when eGRF is reduced from 60 to 5 ml/min/1,72m2.

2. The average increase of the hemoglobin level after 6-month treatment with different ESAs in predialysis is optimal and varies from 1,1 to 3,1 g/l monthly. The average levels of hemoglobin in the period of supportive treatment of anemia is in the reference borders in patients treated with all ESAs.

3. The average doses of rapid-acting ESAs in predialysis during the first 6 months of treatment are comparable. Completely comparable are the average doses of long-acting ESAs. A significant decrease in the average monthly doses of all drugs is found during the second 6-month period of treatment of RA in predialysis and additional decrease in the period of treatment after the 12^{th} month in four out of five ESAs.

4. Correction of RA with ESA in predialysis is effective in all patients with different main diseases. The hemoglobin level is increased significantly in all etiological groups in the first 6-month period of treatment.

5. Duration of HDT is significantly higher in patients with previous anemia treatment which allows us to accept that the better hematological markers at the beginning of HDT, especially in this group of patients define better survival rate.

6. Patients with previous renal anemia treatment at the beginning of HDT have a considerably better RF compared to the patients who did not undergo such treatment. All differences give enough evidence to support the necessity of treatment of RA in predialysis period of all patients with CKD.

7. The dose of epoetin progressively decreases almost trice during the period from 6th to 48th month of treatment with PD. The differences between the average epoetin doses for these 6-month periods are significant.

8. The average value of hemoglobin increases gradually from the beginning of treatment to the 24th month in hemodialysis and to 18th month in treated with PD, when it reaches the recommended therapeutic target from 110 to 120 g/l. Because of the more severe renal dysfunction and the odd character of HDT, anemia correction during this treatment is slower than the predialysis period and than in PD.

9. Anemia correction is significantly better in patients treated with PD, compared to patients treated with HD. This is accomplished with lower doses of ESA, which defines lower financial costs.

10. Before initiation of treatment of RA in predialysis QL is with comparable score for both genders. After 6-month treatment of RA with epoetin in predialysis an increase of the score of QL in all domains is found, which varies from 12,7 to 40,2%. The increase of QL is better in males.

11. In patients from both genders, undergoing dialysis treatment of CKD, QL is equal. In 12/19 domains the scores in males and females are completely comparable. In all domains the differences between the average values of the scores of QL in patients from both genders are insignificant.

12. All patients with CKD – in predialysis and undergoing dialysis treatment score constantly, in all time intervals and equaly high QL in two domains – “Support from the medical staff” and “Satisfaction from treatment”. Major part of the patients who undergo hemodialysis treatment, primarily males, refuse to evaluate QL in the domain for sexual function.

6. Contributions

6.1. Original contributions

1. For the first time a simultaneous study of the treatment of renal anemia with ESA in patients with CKD in predialysis and treated with hemodialysis and peritonela dialysis is conducted.

2. For the first time a study on treatment of renal anemia in CKD is conducted, that compares results of application of five ESAs.

3. For the first time it is found that treatment of renal anemia in CKD in predialysis is performed primarily in patients aged 60 to 80 years.

4. For the first time the average duration of renal anemia treatment with different ESAs is calculated, and based on that the efficacy of each drug is studied.

5. For the first time we found that with the increase of the duration of dialysis treatment increases the relative share of patients in whom epoetin treatment temporary terminated – up to 20% in hemodialysis and up to 40% in patients on peritoneal dialysis.

6. For the first time it is found that treatment of renal anemia in predialysis defines significantly longer duration of the following dialysis treatment.

7. For the first time it is found that in all patients with CKD – in predialysis and on dialysis treatment, score continuously and equally high the QL in two domains – “Support from the medical staff” and “Satisfaction from treatment”.

8. For the first time it is found that after 6-month treatment of renal anemia with epoetin in predialysis QL is increased in all domains with 12,7 to 40,2%.

6.2. Confirmatory contributions

1. The relation between renal function and severity of renal anemia in CKD is confirmed.

2. It is confirmed that correction of renal anemia is completely effective in all studied groups in the period at the beginning of treatment – during the first six months in predialysis and the first eighteen months in treated with peritoneal dialysis.

3. It is confirmed that the optimal support of the level of hemoglobin in all studied groups in predialysis and in treated with dialysis in the recommended from Bulgarian and foreign instituttions target.

4. It is confirmed that correction of renal anemia and support of target levels of hemoglobin in patients with CKD is realized respectively with small and average doses of ESA.

5. It is confirmed that renal function is stabilized in treated with ESA in predialysis as in part of the patients it is improved, and in all of them there is no worsening after six and twelve months from the beginning of treatment.

6. It is confirmed that treatment of renal anemia in CKD is more successful with lower doses of ESA and with achieved higher levels of hemoglobin in treated with peritoneal dialysis, compared to treated with hemodialysis.

7. It is confirmed that treatment of renal anemia is equally effective in patients with different main diseases in both predialysis and dialysis stage.

8. It is confirmed that QL is equal in patients with CKD from both genders in predialysis and in dialysis stage. In both groups there are no domains with severely low results and respectively – very poor QL.