Review article

Chronic Kidney Disease Related Anemia - A Narrative Review

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Abstract

Iron is one of the most important essential elements, required by every cell in the body. Anemia is one of the most common medical conditions, defined as a decrease in blood's ability to transport oxygen to tissues, resulting in tissue hypoxia. However, anemia is not a disease, but rather the manifestation of an underlying disorder or disease and it is an important clinical marker of a disorder that may be basic or something more complex. Therefore, once anemia has been diagnosed, the physician must determine its exact cause.

Anemia is frequently associated with chronic kidney disease (CKD) as a consequential disorder of iron metabolism and erythropoiesis regulation. It is a result of a relative erythropoietin deficiency, functional iron deficiency, impaired iron absorption, or blood loss due to dialysis. CKD related anemia is associated with an increased risk of morbidity and mortality. Given the importance of public health, it is necessary to raise CKD awareness, and to encourage early diagnosis and treatment. The recommendations and guidelines of all professional societies of nephrology emphasize early diagnosis and timely treatment. It is important to ensure that patients have a good quality of life while also minimizing the risks of further complications associated with anemia.

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Introduction

Iron is involved in many cellular processes and is one of the most important minerals in the body. Its absorption, transfer and metabolism are strictly regulated. Most of the ironin the human body, about 60-70%, is embedded into the erythrocyte hemoglobin, while ferritin and hemosiderin account for 20-30% of iron reserves in hepatocytes and macrophages of the reticuloendothelial system (1). Minimal content of iron is found in myoglobin or is embedded into various enzymes. Transferrin is a transport protein in plasma and approximately 3 mg of iron is bound to it. The body of an adult contains 3-5 g of iron, with the most of the circulating iron, about 18-20 mg per day, spent on the synthesis of hemoglobin in erythroblasts.This article is written as a narrative review that provides synthesis of knowledge and applicability of results of recent and significant studies to practice.

Disorders of iron homeostasis

Anemia is one of the most common medical conditions, because it is a symptom of another disease in more than 50% of the cases. The most common causes of anemia are: decreased production, increased deterioration or loss of erythrocytes. Decreased erythrocyte production is caused by weakened bone marrow, either due to a lack of bone tissue or due to suppressed inflammatory or tumor cells. Erythropoietin is a hormone that stimulates the production of erythrocytes and its low levels may result inanemia (2). The main causes of such anemia are decreased production and excretion of erythropoietin (EPO) from the kidneys and a reduced erythropoietic response to EPO (2).

What causes anemia development in CKD and what consequences does it bring?

CKD is a long-term condition with progressive impairment of renal function. Symptoms develop in stages, and they can generally include fatigue, nausea, vomiting, stomatitis, anorexia, muscle twitching, cramps, peripheral neuropathy, convulsions, and itching. Anemia occurs in addition to this wide range of symptoms. CKD develops as a result of any condition that causes functional kidneyimpairment of sufficient duration and intensity; thus the cause of its development can be diabetic nephropathy, hypertensive nephroangiosclerosis, primary and secondary glomerulopathiesinterstitial disease, etc.

Metabolic syndrome associated with arterial hypertension and type 2 diabetes is a major cause of renal dysfunction (3).

CKD involves five stages of kidney damage. In stage 1 CKD, eGFR > 90 mL/min/1.73 m2 signifies normal glomerular filtration, but there are other signs of kidney damage, such as proteinuria or erythrocyturia. In stage 2, the eGFR is between 60 and 89 mL/min/1.73 m2, and stage 3 includes 3.a.) a stagein which the eGFR is between 45 and 59 mL/min/1.73 m2, and 3.b.) a stage in which the eGFR is between 30 and 44 mL/min/1.73 m2, when severe symptoms appear, e.g., swelling of extremities, back pain, high blood pressure and anemia. In stage4 of the disease, the eGFR is between 15 and 29 mL/min/1.73 m2, which indicates severe kidney damage in addition to the previously described symptoms. Stage 5 CKD indicates end-stage renal failure and eGFR is <15 mL/min/1.73 m2 (4). Symptoms ofrenal failure are itching, nausea, vomiting, swelling of the extremities, pain and problems urinating, breathing and sleeping. In this stage of the disease, the patient is forced to undergo kidney dialysis or, if possible, a kidney transplant. Normocytic normochromic anemia occurs in the early stages of CKD, andit is an important factor in the development of cardiovascular disease. The cause of anemia is erythropoietin deficiency. As renal tissue function is slowly lost, erythropoietin secretion decreases, and advanced renal impairment contributes to the severity of anemia. Symptoms of anemia appear when GF drops below 60 mL/min in men and below 50 mL/min in women. Acute anemiaspresent more severe symptoms than chronic anemias, because there is less time for the organism to adapt. Significant symptoms, such as shortness of breath,

weakness, fatigue, headache, loss of concentration orpalpitations, occur when hemoglobin is less than 90 g/L.

Iron accumulation disorders, which represent a heterogeneous group of hereditary and acquired disorders, are at the opposite end of the spectrum of iron metabolism disorders. Iron overload can lead to the formation of reactive oxygen species (ROS), which can damage many cellular components (5).

Impairediron recycling, mediated by the liver hormone hepcidin, leads to the second most common anemia: inflammatory anemia (IA) or chronic disease anemia (CDA). Inflammatory anemia (IA, formerly referred to as chronic disease anemia or chronic disorder anemia) is usually a mild to moderate anemia (hemoglobin rarely below 8 g/dL) that develops as a result of an infection, inflammatory disease or cancer. It differs from iron deficiency anemia in that iron stores are preserved in the marrow of macrophages, in the spleen and in the liver, which recycle obsolete erythrocytes. Accordingly, inflammation anemia signifies a disorder of iron distribution. IA includes low serum iron levels despite adequate systemic iron stores (6). There are three mechanisms of inflammatory anemia, which include: a slight shortening of erythrocyte lifespan, a decrease in erythropoiesis due to a decrease in EPO secretion, a poorer bone marrow response to erythropoietin and impaired cellular iron metabolism.

Anemia in CKD patients

CKD diagnosisis based on laboratory indicators of renal dysfunction, imaging methods and renal biopsy. Anemia is very common in patients with CKD and is the result of dysregulation of iron metabolism and erythropoiesis. It occurs as the result of relative erythropoietin deficiency, functional iron deficiency, impaired iron absorption, or blood loss due to dialysis. Chronic renal patients with anemia have increased levels of serum hepcidin-25. Patients with CKD suffer from both absolute and functional iron deficiency. Absolute iron deficiency is defined by severely reduced or absent iron stores, while functional iron deficiency is defined by adequate iron stores but insufficient iron availability for incorporation into erythroid precursors, as a result of elevated hepcidin levels. Absolute iron deficiency is defined when transferrin saturation (TSAT) is ≤20% and serum ferritin concentration is ≤100 ng/mL among dialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. Functional iron deficiency is characterized by TSAT ≤20% and elevated ferritin levels.

Treatment

The treatment of anemia in patients with CKD is based on guidelines. The KDIGO (Kidney disease: Improving Global Outcomes) group has published treatment guidelines for anemia in chronic renal patients, and the ERBP (European Renal Best Practice) group has reviewed those guidelines. The Croatian Society for Nephrology, Dialysis and Transplantation (HDNDT) has published its own guidelines based on the recommendations and experiences of European and international professional societies, as well as its own. In all cases of CKD or anemia, the following needs to be checked: erythrocyte count (E), hemoglobin concentration (Hb), erythrocyte mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH),mean corpuscular hemoglobin concentration (MCHC), leukocyte count (L), platelet count (Plt), absolute reticulocyte count (Rtc), serum ferritin concentration, plasma transferrin saturation (TSAT) and levels of vitamin B12, and folic acid (7).ESA should be used with caution by people who have a history of cancer or stroke. These conditions are not absolute contraindications to the use of ESA, and the decision should be made with the patient's consent, taking the risks and benefits of the treatmentinto account.

It is recommended that Hb levels are maintained between 100 and 120 g/Lin adults and between 110 and 120 g/Lin children (7).

Formula for calculating iron requirements:

Iron (mg) = body mass (kg) x desired Hb concentration (g/L) - current Hb concentration (g/L) x 0.24 +amount to replenish the iron stores

(adults 500 mg, children 15 mg/kg of body mass) (7).

Table 1. Main causes of CKD

Cause	Example
High blood pressure	Malignant glomerulosclerosis
(hypertension) and diabetes	Nephroangiosclerosis
Glomerulopathies	Primary focal glomerulosclerosis
	Idiopathic crescentic GN
	IgA nephropathy
	Membranoproliferative GN
	Membranous nephropathy with systemic diseases
	Amyloidosis
	Diabetes
	HUS
	Postinfectious GN
	SLE
	Wegener's granulomatosis
Chronic tubulointerstitial nephritis	
Hereditary nephropathies	Alport's syndrome
	Medullary cystic disease
	Nail-chip syndrome
	Polycystic nephropathy
Urinary tract obstructions by kidney stones, enlarged prostate or cancer	BPH
	Urethral obstruction (congenital, stones, malignancy)
	Vesicourethral reflux
Renal macrovascularopathy (artery and vein)	
Nephrotic syndrome	
Recurrent kidney infection (pyelonephritis)	
Lupus and other immune system diseases including polyarteritis nodosa, sarcoidosis, Goodpasture syndrome and Henoch-Schonlein purpura	

Table 1. lists the main causes of CKD (8)

Filtered erythrocytes should be used as needed. Blood transfusion should be used in case of inadequate response to ESA treatment and in cancer patients at risk for ESA treatment, in case the risk outweighs its benefit. It is not recommended to use blood transfusions based on Hb levels, but only in the presence of symptomatic anemia, and it is recommended in acute conditions in cases of bleeding, unstable angina pectoris and in perioperative patient care. Due to the very narrow therapeutic range in which the Hb concentration should be maintained and large individual differences between the patients and the methods of renal function replacement, it is very difficult to maintain the Hb concentration within the set limits.

Epoetin Therapy

The introduction of erythropoietin (EPO) into clinical practicefundamentallyaltered the care of patients with CKD.The extensive use of EPO and its analogues (erythropoietin-stimulating agents, ESAs) for the purpose of anemia correction has resulted in reducing associated morbidity and improving functionality, exercise tolerance, cognitive function, and overall quality of life(9).Patients who develop pure isolated red cell aplasia (PRCA) after treatment with any erythropoietin should not receive Epoetin alfa (10). Increased incidence of thrombotic vascular events (TVD) has been observed in patients receiving drugs to stimulate erythropoiesis. These include venous and arterial thrombosis and embolism (including some fatalities), such as deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, and myocardial infarction. In addition, cerebrovascular events have been reported (including stroke, cerebral hemorrhage, and transient ischemic attacks) (11).

Darbepoetin alfa

Darbepoetin alfa is a second-generationESA that is a supersialylated analogue of EPO, possessing two extra N-linked glycosylation chains. This property confers a lower clearance rate in vivo, and the elimination half-life of the compound in humans after a single intravenous administration is 25.3 hours versus 8.5 hours for epoetin alfa. It has a 3-fold longer serum half-life compared to epoetin alpha and epoetin beta. It stimulates erythropoiesis (increases red blood cell levels) by the same mechanism as rHuEpo (binding and activating the EPO receptor) and is used to treat anemia commonly associated with CKD and cancer chemotherapy (12).

Methoxy Polyethylene Glycol – Epoetin Beta (CERA)

Alternative bioengineering techniques for extending the half-life of EPO resulted in the development of CERA, a continuous erythropoietin receptor activator. The drug stimulates erythropoiesis by interacting with the erythropoietin receptor on progenitor cells in the bone marrow.CERA has an elimination half-life in humans that is considerably longer than the half-life of either epoetin or darbepoetin alfa (13).Stage 4 studies suggest that many patients are able to be maintained with monthly administration of CERA, and a superiority study suggests greater efficacy with this frequency of administration compared with monthly dosing of darbepoetin alfa when administered intravenously to hemodialysis patients.

Effects of therapy in CKD

In CKD, other causes of anemia must be corrected before initiating epoetin therapy. If the serum ferritin concentration falls below 100 ng/mL, it is necessary to introduce iron therapy. It is best to give intravenous iron, although oral administration can also be considered in patients not yet on dialysis. In Time to Reconsider Evidence for Anaemia Treatment (TREAT's) largest Essential Safety Arguments (ESA) study, initiating ESA therapy in patients with mild anemia underwent a benefit – risk assessment and was found to be unfavorable due to a small increase in quality of life, and high possibility of stroke (14). Based on research, The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the introduction of ESA therapy when the hemoglobin concentration falls below 9 g/dL. The commonly used target range of hemoglobin is

between 10 and 12 g/dL. The usual initial intravenous or subcutaneous dose of epoetin is about 25 to 50 IU/kg two or three times a week, of darbepoetin alfa 20 to 30 mcg once a week, and of C.E.R.A. 30 to 60 mcg once every two weeks. An increase in reticulocytes (RTC) is observed 3 to 4 days after startingthe therapy, and an increase in hemoglobin of about 1 to 2 g/dLis observed during one month. It is not recommended to increase the hemoglobin level to 13 g/dL; instead, the limit should be at 11.5 g/dL (15).

Hyporesponsiveness to ESA therapy

According to the latest recommendations, hyporesponsiveness to ESA therapy occurs when the Hb concentration does not respond by increasing in the first month of ESA treatment using modified weight-based dosages, or if, after treatment with stable doses, the patient's ESA dosage is changed two times up to 50% of the dose previously used, and that earlier dose achieved a stable condition. The usualcauses of hyporesponsiveness are iron deficiency, infection or inflammation and underdialysis. If possible, the causes of hyporesponsiveness must be treated and corrected. For example, if there is a possible iron deficiency, the patient should receive iron treatments intravenously. Using laboratory tests, it is possible to establish if a patient has severe hyperparathyroidism, or a deficiency of vitamin B12, folate and thyroxine. Hb electrophoresis should be performed to rule out hemoglobinopathies as causes of resistance to ESA therapy. Some patients taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers may be expected to require a higher dose of ESA treatment, but it is rarely necessary to stop taking these drugs. If a primary bone marrow disorder is suspected, a hematological examination of the bone marrow sample should be performed. A bone marrow test is also performed when antibody mediated PRCA are suspected, although a reticulocyte test and antibody to EPO measurement can be performed prior to this test. If a patient receiving ESA therapy has a high count of RTC, the bone marrow produces more new erythrocytes than necessary. Bleeding or hemolysis should be investigated by endoscopic examination or hemolysis test (serum bilirubin, Coomb's test,LDH - lactate dehydrogenase and haptoglobin levels).

The maximum dose of the drug is not precisely defined and doses of 60,000 IU EPO per week are commonly used in the United States. There are indications that high doses of the drug may increase the side effects regardless of Hb concentration. Experience has shown that very high doses can be effective even in critical patients, butRTC indicate no reduction in transfusion requirements and a rise in deep vein thrombosis. Given all that, it seems reasonable to continue with the same dose of ESA (16).

Pharmacotherapy using Roxadustat

Roxadustat, a new drug approved in Japan and China, is used in the treatment of anemia and it reacts as hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PH), thus increasing endogenouserythropoietin production, which stimulates the production of hemoglobin and erythrocytes. Roxadustat activates a response that occurs naturally when the body responds to reduced blood oxygen levels. Roxadustat promotes erythrocyte production by increasing endogenous erythropoietin production, improving the absorption, transport and utilization of iron and reducing hepcidin regulation, which helps overcome the negative impact of inflammation on hemoglobin synthesis and production of erythrocytes (17).

Studies

A list of studies conducted in CKD patients with anemia can be found on the website https://clinicaltrials.gov/(18). A total of 337 studies were found for Anemia in Chronic Kidney Disease, five of which are currently active and are listed in Table 2.A total of 243 studied were completed. Table 3. shows the first 30 completed studies involving different countries of the world (18). Insights provided by these medical research promises to lessen the impact of anemia in CKD patient by making sure that existing treatments are used in the best possible

ways. Research can find answers to things that are unknown, filling gaps in knowledge and changing the way that health care professionals work and ultimately improving CKD patient treatment and care.

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Table 2. List of studies conducted in chronic renal patients with anemia, ClinicalTrials.gov (16)

Row	Status	Study title	Conditions	Interventions	Locations
1.	Active, not recruiting	Study of HEMAX PFS Versus EPREX/ERYPO® in Predialysis Chronic Kidney Disease	Anemia in Chronic Kidney Disease	Biological: Erythropoetin alfa	• CEMEDIC Buenos Aires, Argentina • CEREHA Buenos Aires, Argentina • CIMEL Buenos Aires, Argentina • And 8 more…
2.	Active, not recruiting	Ascertain the Optimal Starting Dose of Mircera Given Subcutaneously for Maintenance Treatment of Anemia in Pediatric Patients With Chronic Kidney Disease on Dialysis or Not Yet on Dialysis	Anemia, Renal Insufficiency, Chronic	Drug: Mircera	• University of Alabama at Birmingham; Pediatric Nephrology Birmingham, Alabama, United States • Loma Linda University Health, Loma Linda, California, United States • Emory University School of Med; Pediatrics Atlanta, Georgia, United States • And 19 more…
3.	Active, not recruiting	Desidustat in the Treatment of Anemia in CKD	Chronic Kidney Disease Stage 3, Anemia, Chronic Kidney Disease Stage 4, Chronic Kidney Disease Stage 5	Drug: Desidustat oral tablet Drug: Darbepoetin Alfa	• Sunrise Hospital Vijayawada, Andhra Pradesh, India • Max Super Specialty Hospital New Delhi, Delhi, India • Thakershey Charitable trust Hospital Ahmadabad, Gujarat, India • and 29 more
4.	Active, not recruiting	Acute Effects of Intravenous Iron on Oxidative Stress and Endothelial Dysfunction in Non-dialysis CKD	Renal Anemia, Iron Toxicity, Oxidative Stress, Endothelial Dysfunction	Drug: Sodium Chloride 0.9% Intravenous Solution, Drug: Ferinject	• "Dr. Carol Davila" Teaching Hospital of Nephrology Bucharest, Romania
5.	Active, not recruiting	Prospective Observational Study of Erythropoietin- Iron Interaction in Anemia of Renal Disease	Anemia of End Stage Renal Disease	Other: Specimen collection	• University of Louisville, University Kidney Center Louisville, Kentucky, United States • Western New England Renal and Transplant Associates Springfield, Massachusetts, United States • Duke University Durham, North Carolina, United States

Table 3. List of completed studies, showing the first 30 completed studies involving different countries of the world.

Row	Study title	Conditions	Interventions	Locations
1.	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis	Anemia in Chronic Kidney Disease in Non-dialysis Patients	Drug: Roxadustat Drug: Placebo	Site BY37503 Brest, Belarus Site BY37504 Gomel, Belarus Site BY37501 Grodno, Belarus And 135 more…
2.	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa	Anemia in Chronic Kidney Disease in Non-dialysis Patients	Drug: Roxadustat Drug: Darbepoetin alfa	Site AT43009 Vienna, Austria Site BY37503 Brest, Belarus Site BY37501 Grodno, Belarus (and 122 more…)
3.	ASP1517 Phase 2 Clinical Trial - Double-Blind Study of ASP1517 for the Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis	Anemia in Chronic Kidney Disease Patients Not on Dialysis	Drug: ASP1517 Drug: Placebo	Chubu, Japan Hokkaido, Japan Kansai, Japan And 4 more…
4.	Study of FG-4592 in Subjects With Chronic Kidney Disease in China	Anemia in Chronic Kidney Disease	Drug: FG-4592 Drug: Placebo	Peking Union Medical College Hospital Beijing, China Peking University First Hospital Beijing, China Sichuan Provincial People's Hospital Chengdu, China (and 10 more…)
5.	Effect of Hemodialysis on the PK of JTZ-951 in Subjects With End-stage Renal Disease	Anemia in Chronic Kidney Disease	Drug: JTZ-951	Minneapolis, Minnesota, United States

6.	A Non-interventional Study of Diafer in Subjects With CKD on Haemodialysis for Treatment of Iron Deficiency	Anemia in Chronic Kidney Disease	Drug: 5% Iron Isomaltoside 1000	Heleneholmsdialysen Malmö, Sweden Morriston Hospital, Renal Department Swansea, Wales, United Kingdom
7.	Strategies Using Darbepoetin Alfa to Avoid Transfusions in Chronic Kidney Disease	Anemia in Chronic Kidney Disease Patients Not on Dialysis	Biological: Darbepoetin alfa Other: Placebo	Research Site Anniston, Alabama, United States Research Site Birmingham, Alabama, United States Research Site Huntsville, Alabama, United States And 246 more…
8.	TARGTEPO Treatment for Anemia in Chronic Kidney Disease (CKD) Patients and End-Stage Renal Disease (ESRD)	Chronic Kidney Disease, End-stage Renal Disease	Biological: MDGN201 TARGTEPO	Barzili Medical Center Ashkelon, Israel Meir Medical Center Kfar Saba, Israel Medical Center of the Galilee Nahariya, Israel (and 2 more…)
9.	A Study of FG-4592 for the Treatment of Anemia in Chronic Kidney Disease Patients Not Receiving Dialysis	CKD Anemia	Drug: FG-4592 Drug: Placebo	Investigational Site Huntsville, Alabama, United States Investigational Site Tempe, Arizona, United States Investigational Site Alhambra, California, United States (and 142 more…)
10.	Safety and Tolerability of FCM vs Standard of Care in Treating Iron Deficiency Anemia in Chronic Kidney Disease Patients	Anemia	Drug: Ferric Carboxymaltose Drug: Standard Medical Care (SMC)	Luitpold Pharmaceuticals Norristown, Pennsylvania, United States

11.	Comparison of Darbepoetin Alpha and Recombinant Human Erythropoietin for Treatment of Anemia in Children With Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Recombinant human erythropoietin Drug: Darbepoetin Alfa	Sir Ganga Ram Hospital New Delhi, Delhi, India
12.	A Pilot Study of KRX-0502 (Ferric Citrate, Administered Without Food, in Treating Iron-deficiency Anemia	Anemia of Chronic Kidney Disease	Drug: KRX-0502	Barzilai Medical Center Ashkelon, Israel, Western Galilee Hospital Nahariya, Israel, Nazareth Hospital-EMMS Nazareth, Israel
13.	KRX-0502 (Ferric Citrate) for the Treatment of IDA in Adult Subjects With NDD-CKD	Anemia of Chronic Kidney Disease	Drug: ferric citrate Drug: Placebo	AKDHC Medical Research Services, LLC Phoenix, Arizona, United States Southwest Kidney Institute Tempe, Arizona, United States, California Renal Research Glendale, California, United States (and 33 more…)
14.	A Study to Evaluate Efficacy and Safety of JTZ-951 Compared to Darbepoetin Alfa in Korean Renal Anemia Patients Receiving Hemodialysis.	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Darbepoetin Alfa	SMG-SNU Boramae Medical Center Seoul, Korea
15.	Vitamin D as a Modifier of Serum Hepcidin in Children With Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Cholecalciferol	Johns Hopkins University Baltimore, Maryland, United States

16.	Phase 2a Study to Evaluate PRS-080 in Anemic Chronic Kidney Disease Patients	Anemia of Chronic Kidney Disease	Biological: PRS-080#022-DP Biological: PRS-080-Placebo#001	University Hospital Brno Brno, Czechia, HDS - Klaudian's Hospital, Mladá Boleslav, Czechia, Institute of Clinical and Experimental Medicine (ICEM) Prague, Czechia (and 3 more...)
17.	CKD-11101 Phase 3 IV Study in Patients Who Had Renal Anemia Receiving Hemodialysis	Anemia of Chronic Kidney Disease	Biological: CKD-11101 Biological: NESP	/
18.	Effect of Erythropoiesis-Stimulating Agent Therapy in Patients Receiving Palliative Care of Chronic Kidney Disease	Anemia of Chronic Kidney Disease	Drug: Erythropoiesis-Stimulating Agent	Prince of Wales Hospital, Chinese University of Hong Kong Shatin, New Territories, Hong Kong
19.	CKD-11101 Phase 3 SC Study	Anemia of Chronic Kidney Disease	Biological: CKD-11101 (Darbepoetin alfa) Biological: NESP (Darbepoetin alfa)	/
20.	Comparison Study of Two Iron Compounds for Treatment of Anemia in Hemodialysis Patients	Anemia of Chronic Kidney Disease	Drug: Supplementation of ferric carboxymaltose Drug: Supplementation of iron sucrose	Medical University of Vienna, Division of Nephrology and Dialysis Vienna, Austria, Wiener Dialysezentrum GmbH Vienna, Austria
21.	Safety, Tolerability, PK & PD Study of JTZ-951 in Anemic Subjects With End-stage Renal Disease	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Placebo	Lakewood, Colorado, United States Miami, Florida, United States Orlando, Florida, United States (and 2 more...)

22.	Health Care Personnel Time for Anemia Management With Erythropoiesis Stimulating Agents in Hemodialysis Centers in Croatia	Renal Anemia of Chronic Kidney Disease	Other: No intervention	Bjelovar, Croatia Split, Croatia Zadar, Croatia Zagreb, Croatia
23.	A Study to Assess Hemoglobin Level Depending on the Comorbidity Index in Chronic Kidney Disease (CKD) Participants Not in Dialysis Treated With Methoxy Polyethylene Glycol-Epoetin Beta (COMETE)	Renal Anemia of Chronic Kidney Disease	Drug: Methoxy Polyethylene Glycol-Epoetin Beta	CHP Aix Aix En Provence, France Ch Notre Dame Misericorde; Hemodialyse Ajaccio, France Chi D Alencon; Nephrologie Hemodialyse Alencon, France (and 105 more…)
24.	Mass Balance Study of JTZ-951 in Subjects With End-stage Renal Disease on Hemodialysis	Anemia of Chronic Kidney Disease	Drug: JTZ-951, 14C-JTZ-951	Minneapolis, Minnesota, United States
25.	Does Oral Pentoxifylline Administration Improve Hemoglobin in Hemodialysis Patients?	Anemia of Chronic Kidney Disease	Drug: Pentoxifylline	Tanta University Hospital Tanta, Egypt
26.	Study to Evaluate Effect of Lapatinib on Pharmacokinetics of JTZ-951 in Subjects With End-stage Renal Disease	Anemia of Chronic Kidney Disease	Drug: JTZ-951 Drug: Lapatinib	Minneapolis, Minnesota, United States
27.	Periodic Versus Continuous IV Iron Supplementation in HD Patients	Anemia of Chronic Kidney Disease	Drug: Iron Sucrose Supplement	Papageorgiou General Hospital Thessaloniki, Greece

28.	Study of Anemia in Chronic Kidney Disease (CKD) Among High-Risk Hypertensive and Diabetic Patients in Pakistan	Anemia, Diabetes, Kidney Disease, Chronic, Hypertension	/	Islamabad, Pakistan Karachi, Pakistan Lahore, Pakistan
29.	Observational Study of MIRCERA in Users of Self-Application and Multidose Systems	Renal Anemia of Chronic Kidney Disease	Device: MIRCERA	Daun, Germany
30.	Paricalcitol Effect on Anemia in CKD	Anemia, Chronic Kidney Disease	Drug: Paricalcitol Drug: Calcitriol	Federico II University Naples, Italy

Completed studies

Conclusion

Given the importance of CHD for public health, it is necessary to raise awareness of CHD and encourage early diagnosis and treatment. Recommendations and guidelines of all professional nephrology societies are aimed at early diagnosis and timely treatment. When it comes to anemia, the goal is not to correct anemia, but to ensure that the serum hemoglobin level reaches approximately 100 g/L, which can provide the patient with a satisfactory quality of life and minimize the risks related to anemia. The treatment of anemia today represents a largely individualized. It is vital to consider all the current parameters of the disease and condition, the presence of comorbidities, the current method of treatment, as well as the patient's preference.

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