

History of Erythropoietin Stimulating Agents use for the treatment of renal anemia in Poland



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ABSTRACT

One of the first seminal papers that identified kidneys as the source of erythropoietin was published in 1961 by a Polish hematologist Professor Zofia Kuratowska and co-workers from the Warsaw Medical University who performed a series of *in vitro* experiments in isolated mice organs perfused with the blood taken from the hypoxemic animals. Later, a strong position of our country in renal anemia research has been due to an active involvement in nearly all large multicentre clinical studies that led to the approval of epoetins and its analogues. Four Polish centres took part in first European studies on the use of erythropoietin alfa to treat anemia in hemodialysis patients (1988-1989) and in non-dialysis subjects with chronic kidney disease (1990). The success of the studies resulted in the approval of erythropoietin alfa in Poland already in 1989 shortly after its introduction in Europe. The first patient in the world who received in 2001 methoxy polyethylene glycol-epoetin beta in a phase 2 clinical trial was a 44 year old woman chronically dialyzed in Gdańsk. Polish investigators were also involved in the studies with epo-mimetic peginesatide. Poland was also the best-recruiting country in phase 2 and 3 clinical trials with HIF-1 inhibitors. For the last three decades Polish academic nephrologists have published over a hundred articles in the field of renal anemia. Polish nephrologists contributed also to the development of the European guidelines for renal anemia.

KEYWORDS: Erythropoietin stimulating agents, renal anemia, darbepoietin alfa, CERA, EPO-mimetics, inhibitor of prolyl hydroxylase

Anaemia in Polish culture and art

The first mentions of anemia as an ailment appeared out of many historical descriptions and literary works. Historically, the problem of anemia was associated with the poverty, famine and exhausting physical work. The examples of people suffering from anemia were described in the novels, such as "Przedwiośnie" written by the famous Polish novelist and dramatist Stefan Żeromski who became known as the "conscience of Polish literature" (1). The people with anemia were repeatedly mentioned in the literature as thin, sickly and pale (1). Also in the world of art there has been a sign of anemia – the gestalts with abnormal pale complexion, e.g. the famous painting Frenzy of Exultations (Szał uniesień) 1893 by Władysław Podkowiński (1866-1895), and on paintings of Zygmunt Turkiewicz (1913-1973) Reclining Nude or Wojciech Fangor (1922-2015) Gestalts (Postaci).

The treatment of anaemia was for centuries non-specific but widely practised due to high prevalence of this symptom. Folk medicine remedies were simple and mainly based on plants or its extracts. Brews of nettle, wormwood were commonly used. The other common remedy was a milk of mammals. It was believed to improve the general condition. Also a diet rich in meat and fat was believed to be a right treatment for people suffering from general malaise and weakness caused by anaemia (2).

The first information on the treatment of acute anemia with blood products came from the time of January Uprising. Till 1864, the blood products were only used for a massive haemorrhage during military fighting. The first documented blood transfusion in Poland was however the transfusion of blood in the patient after obstetric complications. It took place in the Hospital of the Child Jesus in Warsaw in 1867. The first Polish scientists who published on the treatment of anemia with blood transfusion in patients suffering from anaemia were Dr. Karol Marcinkowski and Dr. Władysław Świątkowski. They later included anemia as an indication to blood transfusion (3, 4).

Zofia Kuratowska (1931-1999) was a Polish scientist and experimental hematologist who played an important role in the discovery of the source of the production of endogenous erythropoietin (Figure 1).

In the 20th century there appeared some ideas that there exists a factor which takes part in the control of the production of blood cells by bone marrow. There were many hypotheses but all early experiments failed to identify the erythropoiesis controlling factor and the source of its production. In 1953 A.J. Erslev proved that there is a humoral factor playing an important role in the process of hematopoiesis and called it erythropoietin (5).



Figure 1 - Zofia Kuratowska (1931-1999) graduate of the Medical University of Warsaw, Polish hematologist, professor, and politician and the first page of her seminal publication from 1961 that proved that the kidneys were the source of erythropoietin.

Although suspected the role of kidneys had stayed virtually unknown yet. There still remained an important question where the erythropoietin is produced or what factors could control its production. Zofia Kuratowska was the first scientist who described in a series of elegant experiments with isolated perfused organs that the main source of erythropoietin is the kidney (Figure 2) (6, 7).

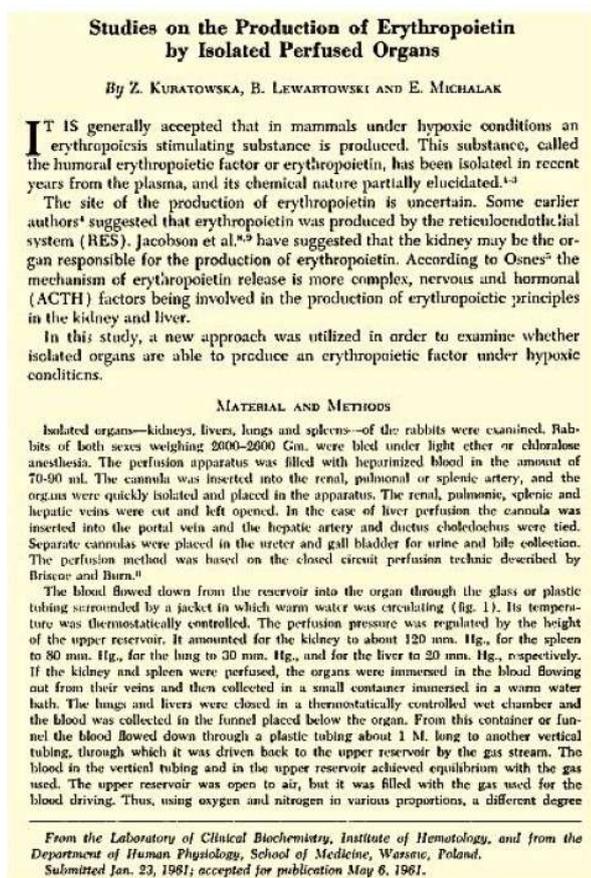


Figure 2 - The first page of the article “Studies on the Production of Erythropoietin by Isolated Perfused Organs” in The Blood from 1961.

The history of therapeutic use of Erythropoiesis Stimulating Agents in Poland

The first large multicentre trial investigating the effects of

epoetin alfa in the treatment of anemia in haemodialysis patients included 4 large academic centres from Poland, i.e. from the Universities of Gdańsk, Katowice, Kraków, and Warszawa. The study was sponsored by Janssen Cilag and 15 adults and 5 children were recruited in Poland. Unfortunately after the completion of the study due to the high price and difficulties with the reimbursement of epoetin the treatment was stopped in the study participants (8).

In 1990 another multicentre trial that investigated the effects of epoetin alfa for in the treatment of anemia in non-dialysis patients with chronic kidney disease was started. The participating centres were Gdańsk, Katowice, Bydgoszcz, Poznań and Zabrze (8).

The trials allowed Polish nephrologists to get more information and experience with the use of ESA. Shortly after the second trial with epoetin alfa was completed this drug was approved under a brand name of Epex in Poland in 1989 (8).

After the political transformation of 1989-1991 that led to the transition from the centralised socialistic system to a market-oriented economy Polish medicine emerged in a poor condition. There were regulatory problems in health care and a scarcity of new drugs and technologies and shortages in medical technologies and drug supplies. In 1990 after endeavours of the leading Polish nephrologist Professor Bolesław Rutkowski and Doctors Janusz Puka, Irena Marcinek and Sławomir Bautenbach Ministry of Health and Social Welfare decided to organise the first centralised purchase of epoetin that was to be distributed to all dialysis units in Poland (8). Shortly thereafter “The national program for the improvement and development of dialysis therapy and kidney transplantation” was introduced. It was the most important step in the development of dialysis therapy and renal anemia treatment. However after its start in 1990 the limited funding allowed to cover epoetin treatment for only 21% of dialysed patients. The percentage of the patients who were treated in the program started to rise in the following years reaching 80% in 1990 when it was terminated and the hospital started to organise local tenders to buy epoetin for their patients (8).

Epoetin beta was initially manufactured by Boehringer Mannheim and approved in Poland under a brand name Recormon in Poland in 1992. From 1997 epoetin beta was manufactured in Poland by Roche. Recormon was later replaced by Neorecormon an improved formulation for subcutaneous use (9). Other epoetins that were also approved in Poland but have never been introduced into clinical use included epoetin omega (Epomax) and epoetin delta (Dynepo) (8).

The significant step in the development of renal anemia treatment was the modification of the molecule of erythropoietin. The modified hyperglycosylated epoetin received the INN name darbepoetin alpha and was also known as the novel erythropoiesis stimulating protein – NESP. Compared to the first generation of unmodified epoetins NESP was characterized by much longer half-life that allowed a reduction of the frequency of administration required for hemoglobin maintenance. The dosing ranged from once weekly to once monthly depending on the stage of chronic kidney disease and individual requirements of the patients (8, 10). Darbepoetin alfa was approved in Poland in May 2004 interestingly on the same day when Poland joined the European Union. It is still distributed in Poland under a brand name Aranesp (8, 10).

In 2004 the licence for epoetin alfa in the European Union expired and the policy of the approval of biosimilar biologic drugs was approved by the European Commission and the European Medicines Agency. That led to the introduction of

biosimilar ESAs that later became available on the Polish market due to the centralized approval procedure for new medicines (8, 11).

The CERA – continuous erythropoietin receptor activator belongs to the third-generation of erythropoiesis-stimulating agents. The molecule is methoxy-polyethylene glycol of epoetin beta and it has a very long half-time that exceeds 130 hours after either intravenous or subcutaneous administration. In 2007 this drug was approved in Poland and launched under a brand name of Mircera (10, 11). Interestingly the first administration in the world of CERA in a phase 2 clinical trial took place in Gdańsk on 7th August 2001. The patient was a 44-year old woman with end-stage kidney disease. In the following years Polish academic centers took part in all large phase 3 clinical trials with this molecule involving both hemodialysis patients and patients with chronic kidney disease not yet on dialysis.

Poland was also very active in clinical trials with other agents that were designed to treat anemia including EPO-mimetics and the inhibitors of prolyl hydroxylase (10, 11). That in particular included the studies with peginesatide which was a small pegylated erythropoietin-mimetic peptide. The clinical trial program resulted in the successful approval of this drug (Omontys) for the treatment of renal anemia in US in 2012. However shortly after its introduction into the market due to the development of severe side effects and the death of several patients caused by the anaphylactic shock peginesatide was withdrawn (12).

The treatment of dialysis patients with renal anemia with ESA became widely available in Poland since 2000 but the drug was at that time fully reimbursed for chronic dialysis patients only. The reimbursement program did not include the patients with chronic kidney disease not yet on dialysis. The treatment of those patients became eventually available in 2012 when a program of the National Health Fund started. The program covers the full cost of the administration of long-acting ESA darbepoetin alpha and methoxy-polyethylene glycol of epoetin beta (Table 1) (11).

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Year	Occurrence
1961	Professor Zofia Kuratowska has described in a series of elegant experiments with isolated perfused organs that the main source of erythropoietin is the kidney
1989	The first large multicenter trial investigating the effects of epoetin alfa (Eprex-Cilag) in the treatment of anemia in hemodialysis patients
1990	The multicenter trial that investigated the effects of epoetin alfa for in the treatment of anemia in non-dialysis patients with chronic kidney disease
1990	The start of the National Program for the Improvement and Development of Dialysis Therapy and Kidney Transplantation that included the stable funding of epoetin for renal anemia treatment.
1990	The first centralized purchase of epoetin for dialysis patients
1992	The approval of epoetin beta under a brand name Recormon
2004	Darbepoetin alfa was approved in Poland under a brand name Aranesp
2007	The approval of methoxy-polyethylene glycol of epoetin beta under a brand name Mircera
2012	The start of the program of the National Health Fund covering the full cost of the administration of long-acting ESAs for the treatment of anemia in pre-dialysis patients

Table 1. The milestones in renal anemia research and therapy in Poland

Polish contribution to renal anemia guidelines

It is important to mention that the Polish nephrologists participated in the development of the guidelines of the diagnosis and treatment of the renal anemia in patients with chronic kidney disease and end-stage renal disease. Professor Bolesław Rutkowski is one of the authors of European Best Practice Guidelines for the management of anemia in patients with chronic renal failure (1999) (13) and Professor Andrzej Więcek took part in the preparation of the Revised European Best Practice Guidelines for the management of anemia in patients with chronic renal failure (2004) (14).