Kidney & Blood Pressure Research

Kidney Blood Press Res 2007;30(suppl 1):2–5
DOI: 10.1159/000107093

Published online: August 27, 2007

Biosimilars and Renal Health Care in the Countries of Central and Eastern Europe

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Introduction

Kidney and Blood Pressure Research currently serves as the official journal of the Czech, Polish, and Hungarian Societies of Nephrology, so the development of renal health care in these countries is of utmost interest for the journal.

As the current supplement of the *Kidney and Blood Pressure Research* is dedicated to many aspects of the manufacturing, immunogenicity, regulations and clinical use of biosimilars, we decided to concentrate our attention only on the potential opportunities and risks of the introduction of biosimilars into clinical practice in the former Communist countries of the Central and Eastern Europe (CEE) which are now the members of the European Union (EU). In addition, as nephrologists we will discuss the relationship between health care and biosimilar use in renal medicine, although similar problems may be partly applicable to other branches of medicines using biopharmaceuticals, e.g. oncology and rheumatology.

Economic Situation in the CEE Countries and Health Care Expenditure

Ten former communist CEE countries (Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia) with altogether more than 100 million inhabitants are now members of the EU. Although the gross domestic product (GDP) in these countries is growing more quickly than in the old countries of the EU, the GDP still remains substantially lower in these new countries (37–86% of the mean of EU) compared with the old ones and there are great differences between countries (table 1). Moreover, the share of the sickness/health care expenditure in GDP is usually lower in new EU countries compared with the old members of the EU (table 2), sometimes less than half of the percentage dedicated to health care in the old EU countries. Unfortunately, there have been no significant increases in the last 10 years and this further compromises the resources available for the health care.

In the last 10 years most of the CEE countries were able to keep the relatively high level of medical care in some aspects almost comparable to the old countries of the EU with considerably lower resources despite very similar costs of both drugs and material probably due partly to the substantially lower personal costs. This mechanism becomes, however, exhausted with the introduction of new diagnostic (e.g. positron emission tomography) and therapeutic (e.g. drug-eluting stents in cardiology) procedures and also with the appearance of new drugs (e.g. tyrosine kinase inhibitors in oncology) including the very expensive biopharmaceutical drugs. As the sharp increase of resources dedicated to health care is not realistic in any of these countries the only practical solution for the payers (mostly insurance companies) is either to lim-

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it the availability of the most expensive therapeutic procedures and drugs, including biopharmaceuticals, only to sometimes poorly defined groups of patients who may benefit most from the treatment, or alternatively (and usually in combination with the previous step) to try to expand the number of treated patients via lowering the cost of the available procedure and/or medication. From this point of view, if biosimilars prove to be safe and cost-effective, a rapid introduction of biosimilars into clinical practice may seem to be an important practical task for the health authorities and the payers (mostly insurance companies).

Renal Health Care in the CEE Countries

There is a long tradition of nephrology in the CEE countries. To name only two, Emmerich Ullmann (1866–1897) from Hungary belonged to the pioneers of renal transplantation and Czech physician Jan Brod (1912–1985) was one of the founders of nephrology as a medical discipline [1].

Also, the origins of the renal replacement therapy in some countries of CEE are relatively old. In the former Czechoslovakia, the first acute hemodialysis was performed in Prague as early as in 1955 and a successful program of renal transplantation was started in 1966 [2]. In Poland, the first hemodialysis was performed in 1958 and a successful transplantation program was also started in 1966 [3].

Unfortunately, economic problems and political isolation of the communist countries of the Soviet block during the 1970s and 1980s resulted in the profound underdevelopment of renal replacement therapy compared with Western Europe. The prevalence of patients receiving hemodialysis, e.g. in Czechoslovakia in 1989, was only about 50 persons per million population compared to about 300 in the EU at the same time. Under the communist regime, the availability of hemodialysis for patients with chronic renal failure was severely restricted with the exclusion or patients older than 50 years, patients with diabetes and patients with systemic diseases (lupus erythematosus) resulting in many patients dying of untreated uremia.

It is not surprising that one of the most prestigious tasks of the health care of many of the CEE countries with a transforming economy especially in the early 1990s was to quickly increase the dialysis capacities to save the lives of as yet relentlessly dying patients. Building of new dialysis units and expanding their capacity increased the access of patients with chronic renal failure to hemodialysis during the last 5–10 years [4–6], but total numbers of patients treated by renal replacement therapy in these CEE countries still remain lower (with the exception of Slovenia) compared to the old EU member countries with a great difference among the countries (278–869 per million population; table 3) [7].

Despite the rapid expansion of the dialysis facilities the economic constraints, however, not very surprisingly still persist and must persist due to the difference in GDP

Table 1. Gross domestic product in purchasing power standards in selected countries of the EU (%)

	1997	2007
EU (27 countries)	–	92.3
EU (25 countries)	100	100
EU (old 15 countries)	110.2	102.9
Bulgaria	25.6	36.4
Czech Republic	69.2	77.6
Estonia	38.4	69.1
Hungary	49.8	64.1
Latvia	33.0	57.3
Lithuania	37.3	57.6
Poland	44.6	53.5
Romania	25.3 (1999; 1997 not available)	39.1
Slovakia	47.4	63.7
Slovenia	71.0	84.9

Reference: http://epp.eurostat.ec.europa.eu.

Table 2. Health care expenditure (% of GDP) in selected countries of the EU

	1994	2004
EU (25 countries)	n.a.	7.4
EU (old 15 countries)	7.4	7.5
Czech Republic	6.3 (1995)	6.7
Estonia	n.a.	4.2
Hungary	n.a.	6.0
Latvia	2.7 (1997)	3.0
Lithuania	4.0 (1996)	3.8
Poland	n.a.	3.8
Slovakia	7.2 (1996)	7.8
Slovenia	5.9 (1995)	5.0

Reference: http://epp.eurostat.ec.europa.eu.
n.a. = Not available.

Table 3. Prevalence of patients on renal replacement therapy in selected countries of the EU (purchasing power standards) in 2004

Country	Total	Hemo-dialysis	PD	Transplant
Bulgaria	339.8[1]	320.7	19.1	missing
Czech Republic	757.6	407.5	33.2	316.9
Estonia	342.2	95.0	54.9	192.3
Latvia	390.4	156.3	48.7	185.4
Poland	536.7[2]	318.8	24.3	193.5
Romania	277.8	202.0	43.0	32.8
Slovakia	498.0	462.5	25.1	10.4
Slovenia	869.3	601.9	59.6	207.8
France	944.7	502.2	46.9	395.6
Germany	997.6	705.1	34.2	258.3
Italy	1,099.3	718.4	98.6	282.3

ERA-EDTA Registry Annual Report 2004. Academic Medical Center, Department of Medical Informatics, The Netherlands, July 2006, http://www.era-edta-reg.org/index.jsp?p=annrep.

PD = Peritoneal dialysis.

[1] Data include dialysis patients only.

[2] Data refer to the year 2005.

and health care expenditure described above. As the cost of dialysis equipment and all resources and drugs is in principle the same in the old and new EU countries, the quality of care for patients with chronic renal failure cannot be the same in CEE and old EU countries despite important savings achieved by the still much lower salaries of the health personnel in the former communist countries.

Although the availability of dialysis treatment is increasing in some and fully unlimited in some other CEE countries the differences still persist in the number of patients treated by more biocompatible membranes, convective methods, or home dialysis. In parallel, the use of new drugs for the treatment of renal bone disease (e.g. sevelamer, paricalcitol, or cinacalcet) is undoubtedly more restricted in CEE countries compared with the old EU members.

This different standard of treatment was best documented in the treatment of renal anemia. Results of the European Survey on Anaemia Management (ESAM, 2003) [8] documented that 62.9% of Polish patients compared with 23.6–42.4% of patients from the old EU member countries and 32.3% of patients from Slovenia treated by hemodialysis or peritoneal dialysis had serum hemoglobin lower than 11.0 g/dl which was clearly caused by the much lower doses of erythropoietin administered (mean epoetin weekly doses 5,277 IU in Poland compared to 8,523 to 13,006 IU in patients from the old EU countries).

Similarly, analysis of anemia treatment in predialysis patients (PRE-dialysis Survey on Anaemia Management, PRESAM [9]) demonstrated that compared to patients from Western Europe, patients with chronic renal failure from the CEE had lower hemoglobin at start of dialysis (9.8 vs 8.7 g/l, $p < 0.01$), lower hemoglobin at the start of epoetin (8.2 vs. 9.0, $p < 0.01$), lower hemoglobin target levels (11.3 vs. 11.7 g/l, $p < 0.01$) and only 10% of patients in CEE countries compared with 35% of patients from Western Europe started epoetin treatment before the start of dialysis treatment.

So, in conclusion, there is little doubt that the treatment of anemia in patients with chronic renal failure from CEE countries compared to the older EU countries starts later, with lower doses of erythropoietin-stimulating agents (ESAs) and with lower hemoglobin target levels and that the main reason for this difference is the economic constraints.

It is quite understandable that both health care authorities and payers (insurance companies) press the providers using namely economic (lowering the price covered), but sometimes also administrative pressure (e.g. generic prescription) to support the use of generics, e.g. in the treatment of hypertension and hyperlipidemia.

Considering the limited availability of ESAs for patients with chronic renal failure on renal replacement therapy (lower number of treated patients, lower doses given to the treated patients) and very limited availability of epoetins for the predialysis patients, biosimilar epoetins may be clearly viewed by the health authorities and payers as a chance to increase the availability of epoetin and/or target hemoglobin with the same, or even lower cost.

As the CEE countries discussed are currently members of the EU, clinical use of any biosimilar including biosimilar epoetins will have to be regulated by EMEA (European Medicines Agency) guidelines [10]. These regulations will prevent CEE countries from introducing 'not very similar' biosimilars produced outside EU and not registered in EU. On the other hand, as biosimilars are treated by the EMEA in a completely different way compared with generic drugs [see Rossert, this suppl.], the phase III studies required by the EMEA will result in smaller cost savings than expected for biosimilars compared with the experience with synthetic generic drugs [11].

So what are the specific opportunities and risks of biosimilars, if any, in the CEE countries? Although there is potential for the treatment of more patients with chronic renal failure, this expectation may not be fulfilled due to the higher than originally expected costs of biosimilars (additional phase III studies needed) and the competition between different biopharmaceuticals, biosimilars and new low-molecular-weight drugs and new therapeutic procedures across different branches of medicine (e.g. oncology, cardiology and/or rheumatology). In renal medicine itself, there is not only competition between different ESAs, but different treatments and procedures. The cost of treatment of patients with chronic renal failure will tend to increase e.g. due to the introduction of new immunosuppressives, phosphate binders, calcimimetics, etc.

There are clearly also the inherent risks of biosimilars which should somewhat impede the enthusiasm of some payers to use them in clinical practice as early as possible. Learnings from pure red cell aplasia [see Schellekens, this issue] demonstrate that it is especially impossible to predict the long-term risks of only small changes in the production of the biologic drug. Who, except from the producer, will be responsible for the unexpected adverse events? Clearly, the responsibility lies not upon the administration of the hospitals and/or insurance companies, but on the physicians treating the affected patient, although this may not be so apparent in case of forced generic substitution [12].

Some other questions still remain unanswered. With the continuous research in the field of the treatment of renal anemia, new ESAs that have prolonged and more stable effect (e.g. darbepoetin, CERA) have recently been introduced and some other drugs (e.g. inhibitors of HIF prolyl hydroxylase) are eagerly awaited. Will these newer ESAs be classified by the health authorities and payers in the same group (with a potential for the generic substitution) as the classical epoetins?

In conclusion, although the general attitude of physicians to biosimilars will probably be the same in the new and old EU countries, physicians (and also nephrologists) in the new EU countries will clearly be under much stronger pressure by the health authorities and payers to exploit the potential cost savings brought about by the biosimilars. It is important to be aware of the fact that even EMEA regulations cannot relieve physicians from the responsibility of their patients and the patients from possibly experiencing immunologically mediated long-term adverse events which can be only disclosed as early as possible by strict and high-quality pharmacovigilance plans.

Disclosure Statement

Vladimír Tesař has participated as a speaker at meetings and acted as an author for publications sponsored by Amgen. He is a member of the CEE Advisory Board for Amgen.

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