

Investigation of factors influencing the efficacy of erythropoietin therapy in haemodialysed patients

Doctoral theses

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1. INTRODUCTION

Destruction and production of red blood cells should be in balance and adjusted to external demands. These processes are strictly controlled by different cytokines. One of the cytokines playing a role in the differentiation of erythrocytes is erythropoietin (EPO), which in healthy adults prevents apoptosis and promotes further differentiation of bone marrow erythrocyte precursors by binding to erythropoietin receptors (EPOR) located on their surface. This results in the appearance of new and mature red blood cells in the circulation as well as an increase in hemoglobin (Hb) levels, and thus oxygen transport capacity continues to be appropriate.

Erythropoiesis is impaired in patients with chronic kidney disease. Uremia shortens the lifespan of red blood cells by up to 20 to 30 days. On the other hand, endogenous EPO production is decreased or stopped in damaged renal tissue. This may consequently lead to severe, sometimes even life-threatening anemia called renal anemia. In this patient population, treatment should include exogenous EPO replacement in order to achieve a balance between destruction and production of erythrocytes. However, despite of EPO correction, up to 10% of dialyzed patients exhibit decreased erythropoiesis, which means that increasing doses of exogenous EPO are required to maintain the appropriate Hb level, or in more severe cases, Hb levels decrease despite of EPO dose increase. This clinical presentation is known as erythropoietin resistance and influenced by several factors. Among these factors the best known are iron deficiency, vitamin B12 deficiency, chronic inflammatory conditions, secondary hyperparathyroidism, and malignancies. Being aware of these influencing factors is very important, since the severity of renal anemia is related to quality of life and mortality.

The research presented in this thesis is related to factors influencing the efficacy of erythropoietin therapy. First, the correlation between pharmacokinetics and pharmacodynamics of erythropoietin-containing drugs is discussed by using an improved theoretical model. Next the results of two related studies are

presented. Our first publication was on the role of vitamin D in erythropoiesis, therefore this is the first discussed study here. This is followed by a discussion on the single role and combined effects of angiotensin converting enzyme (ACE) gene I/D polymorphism and pharmacological ACE inhibition in the correction of anemia. These studies are presented focusing on the results and conclusions published in the original papers.

2. OBJECTIVES

The aim of my work was to gain further knowledge on the role of vitamin D, ACE inhibition, ACE gene I/D (insertion/deletion) polymorphism, and the combined effect of the latter two on erythropoiesis in dialyzed patients with chronic kidney disease by analyzing clinical data. Further objectives were to review the history of development of genetically engineered recombinant erythropoietin molecules (ESAs = Erythropoiesis-stimulating Agents) and their pharmacological differences arising from structural differences. An existing theoretical model illustrating bioactivity of ESAs in a simple way and meeting current professional challenges had been also extended in this thesis.

2.1. Effect of the EPO molecule and the structure of different ESAs on pharmacodynamic properties

The primary objective of this study was to present the structure, development, and pharmacological properties of different ESAs. A mathematical graphical model was invented in order to assess the effect of the ESA dose administered and the combined effect of two molecular parameters (half-life and receptor affinity) on efficacy and possible erythropoietin resistance. This model was based on a former suggestion, which had been completed with the minimal effective concentration of the individual ESAs. The aim of this study was also to broaden the former theory on minimal effective EPO concentration and, with the help of an explanatory

figure, make it more easily understandable for clinicians and researchers.

2.2. Vitamin D deficiency as a factor in erythropoietin resistance

The primary objective of this study was to find further probative clinical evidences on the role of vitamin D in erythropoiesis. Based on the results of previous studies, it was suggested that vitamin D supply might play a crucial role in the gene-regulated differentiation of erythrocyte precursors. My aim was to prove that vitamin D deficiency constitutes an erythropoietin resistance factor during ESA therapy for renal anemia.

2.3. ACE gene I/D polymorphism, ACE inhibition, and their combined effect on the development of renal anemia

The aim of this study was to better explore and explain the rationale behind the contradictory results of previous studies on the relationship between ACE inhibition / ACE gene I/D polymorphism and erythropoiesis. Therefore, it was evaluated whether efficacy of ESA therapy depends on ACE gene I/D polymorphism and pharmacological ACE inhibition, and how erythropoietin resistance is influenced by the combination of these two factors in dialyzed patients with chronic renal failure. In addition, my aim was to prove that thorough evaluation of the effect of these parameters on erythropoiesis is possible only if these parameters are considered simultaneously.

3. METHODS

3.1. Effect of the EPO molecule and the structure of different ESAs on pharmacodynamic properties

Results of previous international studies were reviewed. Literature search on renal anemia was carried out by using the following search words in PubMed: Red blood cell (RBC),

Biological activity, Erythropoietin (EPO), Erythropoiesis-stimulating agent (ESA), Recombinant human erythropoietin (rHuEpo), Carbohydrate, Sialic acid, Darbepoetin alfa, Glycoengineering, Biosimilar, Follow-on Biologics (FOB), erythropoiesis. Based on the research articles found this way, a brief and to the point summary was made concerning the process of erythropoiesis and the role of erythropoietin in this process.

Together with my colleagues, I invented a graphical theoretical model clarifying the association between EPO half-life / receptor affinity and drug efficacy. This model was based on the previously suggested minimal threshold concentration principle first published by Besarab et al in 1992.

3.2. Vitamin D deficiency as a factor in erythropoietin resistance

Data of 142 hemodialyzed patients with end-stage renal disease were evaluated. Data were obtained from a non-interventional, retrospective, single center (1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary), observational study enrolling patients on chronic dialysis for at least 3 months between 1999 and 2004. Out of the 227 patients chosen in the first round, 85 patients were excluded, since not all data to be analyzed were available at the time of the single cross-sectional data collection. In addition to demographic data, inclusion criteria were the availability of the following data: iron status laboratory values, serum intact parathormone (iPTH) level, serum 25-hydroxycholecalciferol (25(OH)D₃) level, ESA dose, hemoglobin level, serum albumin concentration, and eKt/V, a quality indicator for dialysis. Patients with active hepatitis and those who had been on dialysis less than 3 months were also excluded from the analysis. Blood was taken for laboratory assessments on the mid-week dialysis sessions prior to treatment. For further evaluation of the correlation between hemoglobin levels and ESA dose requirement, the ESA dose/Hb index indicating the degree of erythropoietin resistance was calculated based on the required monthly ESA dose. During the study, all patients received epoetin beta-containing ESA

subcutaneously to reach a hemoglobin level ≥ 10 g/L. Patients also received intravenous iron supplementation (ferrous gluconate) to keep transferrin saturation above 20%. Evaluation of the correlation between Hb, EPO dose and vitamin D supply as well as calculation of pooled data were done by using the SPSS 15.0 software. Patients were assigned into three groups based on their vitamin D supply (< 20 nmol/L; 20 to 40 nmol/L; > 40 nmol/L). Multivariate linear regression model was used for assessing the independent predictors of Hb and the ESA dose/Hb index.

3.3. ACE gene I/D polymorphism, ACE inhibition, and their combined effect on the development of renal anemia

The ACEGENE-BB_HU study was a multicenter (in 11 Hungarian dialysis centers within the dialysis network of B.Braun Avitum Hungary Zrt.), single cross-sectional data collection carried out by the B.Braun Avitum Hungary Zrt. Dialysis Network in 1997. A total of 716 Caucasian patients receiving chronic dialysis treatment for at least 3 months and giving consent to genetic testing were enrolled into the study. Fifty-six patients were excluded from the analysis due to certain conditions influencing their hematological status (severe liver disease, malignancy, hemorrhagic, or hematologic disease at the time of data collection) in order to avoid their effect on erythropoiesis results. Thus 660 patients were allocated into 3 groups based on their genotypes (I/I, I/D, and D/D), and statistical analysis was performed on pooled data of the groups. Additional secondary analyses were carried out for a more exact exploration of the correlations. For this reason, 127 matched pairs were identified including patients with I/I and D/D genotypes. Data collected from the medical records of dialyzed patients were age, gender, time on dialysis, cause of end-stage renal disease, the presence of diabetes, ACE inhibitor therapy, and monthly rHuEPO dose. In addition to demographics and laboratory data, EDTA samples were collected before dialysis, and DNA was isolated from peripheral blood leukocytes for standard non-enzymatic genotyping. Epoetin alfa was used exclusively as erythropoietin therapy. During

data analysis, eventual ACE inhibitor therapy was also considered. Calculation of the erythropoietin resistance index (ERI) was based on the monthly rHuEPO dose/Hb ratio. Statistical analysis was performed by genotype groups using the STATISTICA software (version 10, Tulsa, Oklahoma, USA).

4. RESULTS

4.1. Effect of the EPO molecule and the structure of different ESAs on pharmacodynamic properties

In our summarizing work, we reviewed the process of erythropoiesis and emphasized the basic role of EPO in it, and discussed the role of glycosylation, sialic acid content, and pegylation as important pharmacokinetic factors. We particularly emphasized that in addition to the dose administered, the strength of erythropoiesis induced by exogenous EPO treatment depends on the clearance of the drug, which significantly influences the frequency of dosing. We pointed out that with a certain EPO product, an additional factor, namely product-specific receptor affinity should also be considered for efficacy and clinical use. Consequently, the minimal effective threshold serum erythropoietin concentration is product-specific, which had been demonstrated in two improved graphical models (Figure 1. and Figure 2.).

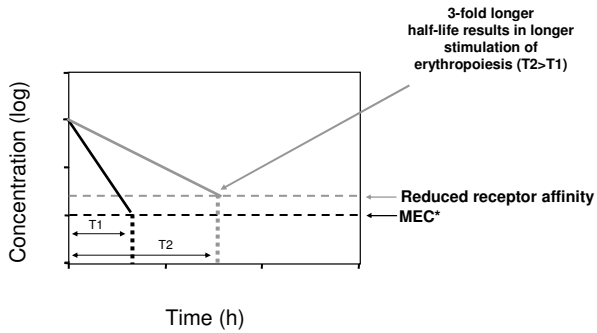


Fig. 1. Model for darbepoetin alfa, which has decreased receptor affinity and longer half-life than rHuEPO. Longer serum half-life of darbepoetin alfa more than compensates for reduced affinity. (*MEC: Minimal Effective Concentration)

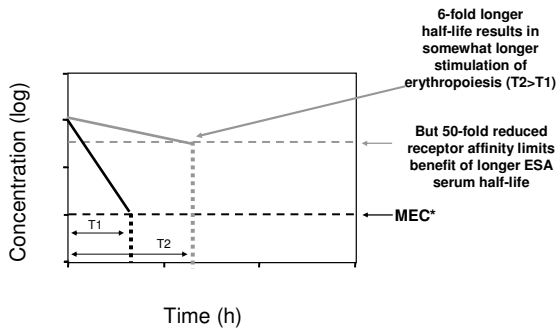


Fig. 2. Dramatically reduced receptor affinity limits gain in biological activity due to longer half-life. (*MEC: Minimal Effective Concentration)

4.2. Vitamin D deficiency as a factor in erythropoietin resistance

Data of 142 dialyzed patients with chronic renal failure were analyzed. Correlation analyses showed significant correlations between serum vitamin D supply and serum Hb levels ($p<0.05$), monthly ESA dose ($p<0.01$), and ESA dose/Hb index ($p<0.01$). Serum hemoglobin levels were also significantly correlated with the quality indicator for dialysis i.e. eKt/V ($p<0.01$), serum albumin concentration ($p<0.01$), as well as transferrin saturation ($p=0.014$). The monthly ESA dose and the ESA dose/Hb index also showed a significant correlation with serum iPTH level ($p<0.05$ for both) and vitamin D supply ($p<0.01$ for both) and a nearly significant correlation with serum albumin level. Based on serum 25(OH)D₃ level reflecting vitamin D supply, 31% of patients were vitamin D deficient (< 20 nmol/L), with a similar prevalence of vitamin D insufficiency (20-40 nmol/L). Serum 25(OH)D₃ level showed an independent positive association with serum Hb level ($p=0.000$) and an independent but inverse association with the ESA dose/Hb index ($p=0.036$) in the multivariate linear regression model with covariates including age, gender, presence of diabetes, serum iPTH, eKt/V, serum albumin, and transferrin saturation.

4.3. ACE gene I/D polymorphism, ACE inhibition, and their combined effect on the degree of renal anemia

The proportion of patients with I/I, I/D, and D/D genotypes were 20%, 41.5%, and 38.5%, respectively. There was no difference in demographics, ESA dose requirement, and laboratory values between the different genotype groups. Hemoglobin levels (95.5 ± 12.0 g/L vs 97.4 ± 13.4 g/L; $p=0.02$) were lower and ESA therapy was more frequent (86.2% vs 75.4%; $p=0.01$) in patients treated with ACE inhibitors. In the different genotype groups, hemoglobin levels in patients not receiving ACE inhibitor therapy were significantly higher in patients with I/D (95.2 ± 11 g/L vs 98.2 ± 11.9 g/L, $p=0.04$) and D/D genotype (93.3 ± 13.2 g/L vs

97.4±14.2 g/L, $p=0.02$). However, no significant difference in hemoglobin levels was observed in patients with I/I genotype (97.9±11.6 g/L vs 95.9±14.9 g/L, $p=0.39$).

In the univariate linear regression model, where hemoglobin was the dependent variable, female gender ($p=0.03$), 5-year increment in dialysis vintage ($p=0.03$) and ACE inhibitor therapy ($p=0.02$) were found to be the significant factors. 10-year increment in age ($p=0.87$), diabetes mellitus ($p=0.12$), and ACE gene I/D polymorphism (I/I and I/D + D/D; $p=0.51$) were non-significant factors. Also, 10-year increment in age and ACE gene I/D polymorphism (I/I and I/D + D/D) were non-significant factors in the multivariate linear regression model ($p=0.84$ and $p=0.51$, respectively). However, female gender ($p=0.02$), 5-year increment in dialysis vintage ($p=0.01$), and ACE inhibitor therapy ($p=0.01$) were significant factors in the multivariate model as well. Differently from the univariate model, diabetes mellitus also had a significant impact ($p=0.04$).

In order to investigate further correlations, matched pairs were identified from a total of 254 patients with I/I and D/D genotype and grouped by ACE inhibitor therapy. Subgroup analysis of the group including all matched pairs ($n=127$ pairs) and the subgroup without ACE inhibitor therapy ($n=62$ pairs) revealed no significant difference between the two genotypes (I/I vs D/D). In patients without ACE inhibitor therapy, higher hemoglobin levels were detected in the D/D genotype group when compared to the I/I genotype group (95.6±14.1 g/L vs 99.0±12.8 g/L; $p=0.14$) despite of the fact that the frequency of rHuEpo therapy was lower in the D/D genotype group than in the I/I genotype group (77.4% vs 69.4%; $p=0.40$); however, the difference in hemoglobin levels was not significant ($p=0.14$). Conversely, in matched pairs with ACE inhibitor therapy, significantly lower hemoglobin levels (98.2±11.9 g/L vs 93.0±12.8 g/L; $p=0.006$) and significantly higher erythropoietin resistance index (ESA dose/Hb) (175.0 [range 116.5-

233.0] vs. 199.1 [range 147.9-250.0]; $p=0.046$) were observed in the D/D genotype group compared to the I/I genotype group.

5. CONCLUSIONS

With the appearance of new ESA products, there is a need in clinical and research communities to improve the theory of minimal erythropoietic threshold concentration. When the first rHuEPOs, the epoetins were introduced, pharmacodynamics of the erythropoietin molecule could easily be estimated based on the dose and half-life, since structure and pharmacological properties of the different products were similar. However, the structures of new ESAs are considerably different from the first rHuEPOs', resulting in differences in pharmacokinetics and bioactivity. Apart from the usual characteristics (half-life, dose, and threshold concentration), the unique and ESA-specific EPO receptor affinity also had to be taken into account during pharmacodynamic modelling. Due to the specific receptor affinity of newer ESAs, the minimal erythropoietic concentration (MEC) characteristic for a certain ESA also changes. Therefore, the different dynamics of ESA-EPO receptor interactions also had to be considered while developing the new model. In this new model, the dose, half-life, and minimal effective threshold concentration reflecting receptor affinity are variable. This improved model was first published by our group, and it makes the correlation between pharmacokinetics and pharmacodynamics as well as bioactivity of different ESAs easily understandable. This model might also help in dose adjustment calculations and in changing the route and frequency of administration of a certain ESA in case of erythropoietin resistance in order to facilitate adequate erythropoiesis.

A significant correlation was found between serum 25(OH)D₃ concentration and erythropoiesis in dialyzed patients with chronic renal failure. Based on our results, the following conclusions were made.

- Serum 25(OH)D₃ concentration shows a positive, significant, and independent correlation with hemoglobin levels.
- Serum 25(OH)D₃ concentration shows a reverse, significant, and independent correlation with monthly erythropoietin dose/hemoglobin ratio.
- Serum 25(OH)D₃ concentration shows a reverse, significant, and independent correlation with the required monthly erythropoietin dose.

The results presented here correspond to the previously published research results. However, they also necessitate a prospective and randomized clinical study, where the significant role of vitamin D supplementation in decreasing erythropoietin resistance in patients with chronic renal failure can be confirmed.

We managed to show several significant correlations between ACE inhibition, ACE gene I/D polymorphism, and erythropoiesis in dialyzed patients with chronic renal failure, which are discussed below.

- With ACE inhibitor therapy, serum hemoglobin levels are significantly lower, and significantly more dialyzed patients require erythropoietin substitution.
- In patients with D/D genotype or D allele, ACE inhibitor therapy results in significantly lower hemoglobin levels than in patients with the same genotype but without ACE inhibitor therapy.
- In unselected patient groups, ACE gene I/D polymorphism itself has no significant influence on erythropoiesis.
- In patients with D/D genotype, pharmacological inhibition of ACE results in a more significant decrease in hemoglobin levels and a more significant increase in erythropoietin resistance compared to patients with I/I genotype.
- With ACE inhibitor therapy, the previously reported, contradictory results on erythropoiesis might be related to

I/D polymorphism of the ACE gene, the pharmacological inhibition of ACE, and the combined effect of these two.

Based on these results, it can be concluded that in the case of erythropoietin resistance, presence of ACE inhibition should always be considered, and genotyping of the patients may especially be important in order to allow for taking into account the combination of genetic and pharmacological effects. This is particularly important in patients with D allele, where erythropoiesis is strongly inhibited by ACE inhibition. It is advisable to consider the presence of these two parameters when planning future studies.

6. LIST OF OWN PUBLICATIONS

6.1. Publications related to this thesis

1. **Kiss Z**, Elliott S, Jedynasty K, Tesar V, Szegedi J. (2010) Discovery and basic pharmacology of erythropoiesis-stimulating agents (ESAs), including the hyperglycosylated ESA, darbepoetin alfa: an update of the rationale and clinical impact. *European Journal of Clinical Pharmacology*, 66: 331-340. (A folyóirat IF értékét Összefoglaló cikk típusú közlemény miatt nem tüntetjük fel.)
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3. **Kiss Z**, Ambrus Cs, Kulcsár I, Szegedi J, Kiss 1 on behalf of the ACEGENE-BB_HU Workgroup. (2015) Effect of ACE gene I/D polymorphism and ACE inhibition on erythropoiesis in patients on hemodialysis. *Journal of Renin Angiotensin Aldosterone System*, 16(4):1021-1027. (IF: 2,4)

6.2. Publications related to the topic of this thesis but not included in the thesis

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4. Monostori P, S Varga I, **Kiss Z**, Kiss I, Haszon I, Papp F, Sümegi V, Bereczki Cs, Németh I, Túri S. (2010) Erythropoiesisstimuláló hatóanyagok és az oxidatív stressz kapcsolata hemodializált betegekben *Hypertonia és Nephrologia*, 14(6): 281-285.
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6.3. Other publications

1. Kiss I, Szegedi J, Kulcsár I, Ambrus Cs, Kerkovits L, Tislér A, **Kiss Z**. 2015Az angiotenzin-konvertáz enzim (ACE) - gén inszerciós/deléción (I/D) polimorfizmusának hatása hemodializált betegek túlélésére. *Hypertonia és Nephrologia*, 19(4): 159-163.
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 16. Révai T, Harnos G, **Kiss Z**. (1999) A diabetesz nefropátia genetikai predispozíciója. *Medicus Universalis*, 32(2): 79-80.
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