ERETHYPOPOIETIN-INDUCED HYPERTENSION IN DIALYZED UREMICS IS INFLUENCED BY GLYCOSYLATION PATTERNS OF THE MOLECULE
S Mihelčič 1, M Mladić 2, D Hadjiyannakos 3, A Anogiatis 2, A Santikou 3, D Vlassopoulos 1, D Hadjiyannakos 1, A Anogiatis 2, A Santikou 3, D Vlassopoulos 1, D Hadjiyannakos 1, A Anogiatis 2, A Santikou 3, D Vlassopoulos 1, D Hadjiyannakos 1, A Anogiatis 2, A Santikou 3
Dept.of Nephrology, Sveti Duh Hospital, Zagreb, Croatia

Recombinant epoetins (Epo) exhibit differences in glycosylation structures. The carbohydrate moieties are essential for the hormone’s action in vivo and appear to have an impact on the potency and pharmacokinetics of the drug. Epo-omega from BHK cells contains less O-glycans and considerably more sialylated N-glycans compared to epo alfa from CHO cells. Hypertension is a common adverse event of epo treatment. In order to assess whether glycosylation patterns of Epo molecules have an impact on epoetin-induced hypertension, we performed a comparative efficacy and safety trial of epo-omega vs. alfa. Sixty dialyzed severely anemic patients (S4±11ys, mean hemoglobin (Hb) 73g/L) were randomized in two groups and treated with epo-omega or alfa for 16 weeks. The initial dose was 2x50IU/kg BW/week for 4 weeks and adjusted thereafter to achieve a stable rise in Hb of 2-3 g/week. The effect of epo-omega vs. alfa on blood pressure was 2x50IU/kg BW/week for 4 weeks and adjusted thereafter to achieve a stable rise in Hb of 2-3 g/week. The effect of epo-omega vs. alfa on blood pressure was 2x50IU/kg BW/week 1-4, whereas Hb steadily increased throughout week 2-12 implicating different mechanisms. Better Hb response on Epo-omega associated with less hypertension in indicated a possible direct role of sugar moieties in inducing hypertension.

O1: Chronic renal failure: anaemia

SERUM STEM CELL FACTOR (SCF) AND ITS SOLUBLE RECEPTOR s-KIT LEVELS IN PATIENTS WITH CHRONIC RENAL FAILURE
Elsayw M.A., 1 Makawy M. A., 2 Abdelmaksoud S.S., 2 Shahin K.Y. 2 and E. Arab S. 2
Department of Internal Medicine 1 and Clinical Pathology 2, Ain Shams University, Egypt

Background; Anemia is almost an invariable presentation of chronic renal failure (CRF). Lack of erythropoietin (EPO) synthesis as well as other contributing factors as reduction of red cell life span and iron and folate deficiency. Proliferation, differentiation, and survival of erythropoietin progenitor cells are mainly regulated by stem cell factor (SCF) and EPO. SCF exerts its biological effects by binding to a specific receptor, the tyrosine kinase c-KIT. SCF and c-KIT play an important role in the development, differentiation, and survival of hematopoietic stem cells. Patients and methods; This study was conducted on 42 patients suffering from various degrees of renal impairment. Group A included 23 chronic renal failure (CRF) patients on regular hemodialysis and group B included 19 patients on conservative treatment. The control group included 21 healthy volunteers. Results; Serum SCF in group of A was higher than group B. However, the difference was not statistically significant. In group B, serum SCF levels correlated directly with parameters of renal function such as BUN and creatinine and correlated inversely with Hb and RBCs. s-KIT levels were significantly higher in group B than the control group. However, no significant difference was found between the former group and group A patients. Also, s-KIT levels were significantly correlated with SCF levels in group B patients. Conclusion; Serum SCF levels are increased with renal function deterioration, which suggests the possibility that the increase in SCF levels may be the result of biological response to renal anemia in patients with EPO shortage.

HOW TO IMPROVE HEMATOLOGICAL PARAMETERS IN PATIENTS WITH CHRONIC RENAL FAILURE USING TOTAL INTRAVENOUS IRON SUPPLEMENTATION IN A SINGLE DOSE
D Vlassopoulos 1, D Hadjiyannakos 3, A Anogiatis 2, A Santikou 3, C Nousias 1, M Sonikian 1, P Papandreou 1, V Hadjiconstantinou 1
1Nephrology, A Fleming Hosp, 2Hematology, Pendeli Pediatric Hosp, 1Aristotelio Renal Unit, Athens Greece

Low red blood cell osmotic resistance (RBCOR) of uncertain origin aggravates dialysis anemia. We attempted to identify factors that influence RBCOR in 55 stable patients dialyzed for more than 6 months (M/F: 35/20), including 20 diabetics. Parameters studied were hematology, biochemistry, plasma osmotic pressure (POP), dialysis strategy, age, sex, time on dialysis (TOD), EPO treatment and RBCOR.

Cuprophane membranes were associated with the most abnormal RBCOR values (Cuprophane: 0.468 ± 0.026 / Synthetic: 0.443 ± 0.025, P=0.002). Patients with abnormal RBCOR had higher EPO needs (r=0.37, P<0.005). 95% of the diabetics had abnormal RBCOR compared to only 31.5% of the non diabetics (r=0.23, P<0.005). In the non diabetic group, normal RBCOR was unfavorably correlated to POP (r=0.48, P<0.002) and higher serum albumin levels r=0.31, P<0.02). In diabetics, RBCOR was unfavorably correlated to POP (r=0.48, P<0.03). In the non diabetic group, normal RBCOR was measured in patients on longer dialysis sessions (0.441±0.030) and on synthetic membranes (0.438±0.024) (values for healthy individuals 0.436±0.010). Abnormal RBCOR, increases the needs for EPO in the dialysis population. Cuprophane membranes, shorter dialysis and higher POP in diabetics adversely affect RBCOR.
NESP (darbepoetin alfa), is a novel erythropoiesis stimulating protein with an approximately 3-fold longer terminal half-life than rHuEPO. The purpose of this study was to evaluate the effectiveness of fixed doses of NESP administered SC once every other week for the treatment of anemia in patients with chronic renal insufficiency (CRI). Eligible patients had a mean baseline hemoglobin (Hb) value <11.0 g/dL, adequate iron stores (TSAT ≥20% or serum ferritin ≥100 ng/mL), creatinine clearance <30 mL/min and had not received rHuEPO (rHuEPO-naive) within the previous 12 weeks. The starting dose of NESP was 0.75 µg/kg rounded to the nearest fixed dose (i.e., 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, and 150 mcg). Dose was titrated, as necessary, to achieve and maintain target Hb (11.0–13.0 g/dL). Analysis of the first 23 enrolled patients to complete at least 10 weeks of NESP treatment showed that the mean (SD) baseline Hb was 9.83 ± 0.73 g/dL and the mean increase in Hb over the initial 4 weeks of NESP treatment was 1.37 ± 0.81 g/dL. The median time to achieve a Hb response (2 consecutive Hb measurements ≥11.0 g/dL) was 6 weeks (range: 0-17 weeks) and 95% of patients reached target Hb range within 10 weeks of initiating NESP therapy (95% CI: 73.2%, 97.6%). At the time of Hb response, the median NESP dose was 50 mcg every other week (range: 30–130 µg). At least one dose adjustment prior to achieving the Hb target range was required by 43% of patients. The safety profile of NESP was consistent with that expected for CRI patients. In conclusion, NESP (darbepoetin alfa) administered as fixed doses once every other week is effective for the treatment of anemia in rHuEPO-naive patients with CRI.
PROINFLAMMATORY CYTOKINES INHIBIT EXPRESSION OF ERYTHROPOIETIN RECEPTOR MESSENGER RIBONUCLEIC ACID
R.-L. Huang, C.-M. Sun, W.-W. Jiang, J.-G. Leu
Division of Nephrology, Department of Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

The influence of inflammatory cytokines on erythropoietin receptor (EpoR) messenger ribonucleic acid (mRNA) expression was detected in a human erythroleukemia cell line (TF-1). TF-1 cells (5 x 10⁶ cells/ml) were incubated with serial dilutions (10 – 200 units/mL) of interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α). EpoR mRNA transcripts in TF-1 cells were inhibited by all three cytokines, with the inhibition increasing with increasing cytokine concentration. The inhibition rates also increased with treatment duration; the maximal inhibition appeared after 16 hours of treatment. After incubation with 200 units/ml of individual cytokine for 16 hours, EpoR mRNA transcripts in TF-1 cells were inhibited by 44.2 ± 1.7% with IL-6 and 49.1 ± 3.8% with TNF-α. Our results show that higher levels of inflammatory cytokines in the sera of hemodialysis patients may be responsible for resistance to EPO therapy.

PLASMA 4-HYDROXYNONENAL AND MALONDIALDEHYDE REDUCTION DURING HAEMODIALYSIS
F Carluccio¹, A Tasco¹, R Craca¹, T Grune², H Hampl³, W Siems⁴
¹Dept. of Nephrology, I. Veris delli Ponti Hospital Scorrano, Italy; ²Clinics of Physical Medicine & ³Dept. of Nephrology, Humboldt Univ. Berlin; ⁴Herzog-Julius Hospital Bad Harzburg; Germany

In Patients with end-stage renal failure undergoing haemodialysis (HD) an imbalance between prooxidative and antioxidative reactions has been described. That was connected with decreases of GSH in red blood cells and increased levels of lipid peroxidation products. In this study the removal of cytotoxic aldehydic lipid peroxidation products such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA) during the haemodialysis was measured in 51 patients. The aldehyde removal was measured in relation to the degree of renal anaemia (group I with Hb<10g/dl, n = 24; group II with Hb>10g/dl, n = 27). Mean plasma concentrations of aldehydic lipid peroxidation products were the following: MDA in group I 1.88 ± 0.35; MDA in group II 1.54 ± 0.38; MDA in controls 0.89 ± 0.21 µM (significant differences: I vs. II p<0.05; I vs. control p<0.01; II vs. control p<0.01); HNE in group I 0.322 ± 0.083; HNE in group II 0.196 ± 0.045; HNE in controls 0.083 ± 0.026 µM (significant differences: I vs. II p<0.01; I vs. control p<0.001; II vs. control p<0.001). During HD MDA and HNE were drastically reduced. MDA was reduced to 1.21 ± 0.43 in group I and to 0.89 ± 0.31 in group II. HNE was reduced to 0.216 ± 0.057, or to 0.140 ± 0.034 µM, respectively. It is concluded, that a) HNE and MDA levels correlate to the degree of renal anemia, b) during HD HNE and MDA are removed by about 40% leading to a protection of proteins and nucleic acids. [Significances were tested by Mann-Whitney rank sum test.]