Epoetin-Alpha: Preserving Kidney Function via Attenuation of Polymorphonuclear Leukocyte Priming

Batya Kristal MD\(^1,5\), Revital Shurtz-Swirski PhD\(^2\), Olga Tanhilevski MD\(^1\), Galina Shapiro MSc\(^2\), Galina Shkolnik MD\(^1\), Judith Chezar PhD\(^3\), Tamara Snitkovsky PhD\(^4\), Meital Cohen-Mazor PhD\(^2,5\) and Shifra Sela DSc\(^2,5\)

\(^1\)Department of Nephrology and Hypertension, \(^2\)Eliachar Research Laboratory, \(^3\)Hematology Unit, and \(^4\)Biochemistry Laboratory, Western Galilee Hospital, Nahariya, Israel

\(^5\)Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

**Key words:** epoetin-alpha, erythropoietin receptor, inflammation, oxidative stress, polymorphonuclear leukocyte priming

---

**Abstract**

**Background:** Polymorphonuclear leukocyte priming and low grade inflammation are related to severity of kidney disease. Erythropoietin-receptor is present on PMNLs.

**Objectives:** To evaluate the effect of 20 weeks of epoetin-alpha treatment on PMNL characteristics in relation to the rate of kidney function deterioration in patients with chronic kidney disease.

**Methods:** Forty anemic chronic kidney disease patients, stage 4-5, were assigned to EPO and non-EPO treatment for 20 weeks. A group of 20 healthy controls was also studied. PMNL priming and PMNL-derived low grade inflammation were estimated, in vivo and ex vivo, before and after EPO treatment: The rate of superoxide release, white blood cells and PMNL counts, serum alkaline phosphatase and PMNL viability were measured. EPO-receptor on PMNLs was assayed by flow cytometry. The effect of 20 weeks of EPO treatment on kidney function was related to the estimated glomerular filtration rate.

**Results:** EPO treatment attenuated superoxide release ex vivo and in vivo and promoted PMNL survival ex vivo. Decreased low grade inflammation was reflected by reduced WBC and PMNL counts and ALP activity following treatment. EPO retarded the deterioration in GFR. The percent of PMNLs expressing EPO-R was higher before EPO treatment and correlated positively with the rate of superoxide release. After 20 weeks of EPO treatment the percent of PMNLs expressing EPO-R was down-regulated.

**Conclusions:** These non-erythropoietic properties of EPO are mediated by EPO-R on PMNLs, not related to the anemia correction. A new renal protection effect of EPO via attenuation of PMNL priming that decreases systemic low grade inflammation and oxidative stress is suggested.

**Oxidative stress and inflammation**

Oxidative stress and inflammation are associated with uremia already in the early stages of chronic kidney disease and are involved in the development of atherosclerotic cardiovascular events in this population [1]. Moreover, oxidative stress and inflammation, either acute or chronic, were found to aggravate tubular and interstitial damage and are recognized as mechanisms involved in the progression of chronic kidney disease [1,2]. We recently defined peripheral polymorphonuclear leukocyte priming and related PMNL counts as surrogate markers and key mediators in low grade inflammation and systemic oxidative stress associated with renal failure [3]. The PMNL, one of the main inflammatory cell types, exists in the bloodstream in one of three functional states: quiescent, primed, or activated. Under non-infectious conditions, the PMNLs are quiescent, exhibiting little or no release of reactive oxygen species. Studies have led to the concept of a two-stage activation process: PMNLs first encounter a stimulus that leaves the cells in a “primed” state. Upon encountering a second stimulus, PMNLs proceed to the second state of full activation, releasing reactive oxygen species, granule contents and inflammatory mediators [3]. We have demonstrated a positive significant correlation between PMNL priming, expressed by increased rate of superoxide release, and PMNL counts, implying that the increased PMNL counts in peripheral blood is an adaptive response to PMNL priming [3]. In patients with chronic kidney disease not yet on renal replacement therapy, both PMNL priming and PMNL counts negatively correlated with glomerular filtration rate [3]. PMNL priming and elevated peripheral counts are aggravated as kidney function deteriorates, especially with the commencement of chronic hemodialysis [3].

In previous studies we also showed that epoetin-alpha, beyond its well-known role in anemia correction, possesses non-erythropoietic properties mediated by an EPO receptor on PMNLs [4-6]. Irrespective of the correction of anemia, EPO mediated the alleviation of systemic oxidative stress and low grade inflammation contributed by primed PMNLs in chronic kidney disease patients on dialysis [4,5].

The involvement of oxidative stress and inflammation in the deterioration of kidney function, together with our data on the attenuation of oxidative stress and low grade inflammation by modulating PMNL priming with EPO, prompted us to evaluate the hypothesis that EPO treatment will also slow the rate of kidney failure progression and delay the commencement of renal replacement therapy in patients with kidney disease. We designed a prospective study to evaluate the effect of 20 weeks of EPO treatment on PMNL characteristics and their relation to kidney function deterioration.

**PMNL = polymorphonuclear leukocytes**

**EPO-alpha = erythropoietin-alpha**

**WBC = white blood cells**

**ALP = alkaline phosphatase**

**GFR = glomerular filtration rate**

**EPO-R = EPO-receptor**
function in these patients before initiating renal replacement therapy.

**Patients and Methods**

The study group comprised 40 anemic (hemoglobin 8.1–11 g/dl) chronic kidney disease patients, stage 4-5, before starting renal replacement therapy and EPO treatment. The study was conducted during the period 2000–2001. The patients were divided into two groups: one treated with EPO for 20 weeks (group 1) and the second without (group 2). Group 1 included 20 participants: 4 males and 16 females aged 70.2 ± 2.0 years, with systolic and diastolic blood pressure of 157.1 ± 5.9 and 80.8 ± 2.4 mmHg respectively. The underlying renal diseases were diabetes mellitus (n=7, 35%), hypertension (n=5, 25%), chronic glomerulonephritis (n=2, 10%), polycystic kidney (n=1, 5%), nephrolithiasis (n=1, 5%) and unknown (n=4, 20%). Subcutaneous recombinant human EPO (6000 U/week, EPREX®, Cilag Schaffhausen, Switzerland) was administered for 20 weeks. Only 17 patients completed the 20 week period as 3 were excluded due to non-compliance and commencement of dialysis.

Group 2 included 20 patients – 6 males and 14 females aged 67.2 ± 2.7 years with systolic and diastolic blood pressure of 160.8 ± 5.9 and 85.5 ± 6.1 mmHg respectively. The underlying renal diseases were diabetes mellitus (n=11, 55%), hypertension (n=3, 15%), polycystic kidney (n=1, 5%), chronic glomerulonephritis (n=1, 5%), and unknown (n=4, 20%). Only 11 patients completed their 20 weeks of follow-up without EPO as 9 were excluded mainly due to aggravation of anemia and commencement of dialysis.

All patients received oral maintenance iron supplementation (320 mg/day, ferrous sulfate, slow Fe, Novartis), calcium bicarbonate, statins, beta-blockers, and calcium channel blockers; no patient received angiotensin-converting enzyme inhibitors. Data of serum creatinine levels and PMNL counts 10 weeks prior to starting EPO treatment were taken from the medical files of group 1 patients.

The control group comprised 20 healthy subjects matched for age and gender. The inclusion of these participants was based on a clinical examination with laboratory confirmation. Excluded were patients and healthy controls with evidence of infection, heavy smoking, malignancy, severe hyperparathyroidism or blood transfusions within 3 months before the study. Patients and subjects gave informed consent for blood sampling, which was approved by the institutional committee in accordance with the Helsinki Declaration.

**Blood withdrawal and PMNL separation**

Blood was withdrawn after an overnight fast for biochemical and hematological parameters and for PMNL separation. Ten milliliters of heparinized blood (50 U/ml) was used for PMNL isolation as previously reported [3]. The separated PMNLs (> 98% pure, approximately 10⁷ cells per isolation) were resuspended in a minimal volume (0.1–0.3 ml) of phosphate-buffered saline containing 0.1% glucose, immediately counted, and diluted for the different experimental needs. We defined in vivo conditions where PMNLs were exposed to EPO in the circulation of patients treated with EPO, while in the ex vivo settings separated PMNLs from all subjects and patients were treated with EPO in vitro. Sera were frozen at -20ºC and saved for determination of serum EPO measurements as described below. Blood creatinine levels were measured using Hitachi 917 Automatic analyzer (Boehringer Mannheim, Germany). Kidney function was estimated by the calculated GFR according to the MDRD formula (modification of diet in renal disease) [7].

**Evaluation of PMNL priming**

- **Rate of superoxide release from separated PMNLs.** The rate of superoxide release was assayed after stimulation with 0.32x10⁻⁷ M phorbol 12-myristate 13-acetate (Sigma, St. Louis, MO, USA) as a measure of PMNL priming [3]. The assay is based on superoxide dismutase inhibitable reduction of 80 µM cytochrome C (Sigma) to its ferrous form [8].

- **White blood cells and PMNL counts.** WBC and PMNL counts in blood withdrawn in EDTA were performed by a Coulter STKS counter (Miami, FL, USA).

- **Alkaline phosphatase.** Previous reports have shown that increased plasma ALP activity can serve as a measure of PMNL degranulation derived from PMNL priming [8-10]. Plasma ALP was measured using the Hitachi 917 Automatic analyzer (Boehringer Mannheim).

**Effect of EPO on PMNL functions – ex vivo**

PMNLs from 10 randomly chosen chronic kidney disease patients before starting EPO treatment – with a mean creatinine of 3.7 ± 1.04 mg/dl (range 2.1–5.4), similar to the creatinine range in groups 1 and 2 – were isolated, incubated with EPO and used for the following ex vivo studies.

- **Rate of superoxide release from PMNLs.** Isolated PMNLs were incubated for 15 minutes with increasing concentrations of EPO (0–40 U/ml) (Eprex®,) The rate of superoxide release was determined as described above.

- **PMNL survival.** Separated PMNLs were suspended at 10⁶ cells/ml and incubated in 25% autologous serum at 37ºC for 90 min, with increasing concentrations of EPO (0–40 U/ml). PMNLs were counted by Coulter STKS before and after 90 min of incubation with EPO, with confirmation of cell viability by trypan blue (0.1% w/v) exclusion.

**Levels of endogenous serum erythropoietin**

In both healthy controls and chronic kidney disease patients s-EPO was always measured before EPO treatment was started, using the Human EPO Immunoassay ELISA kit (Quantikine™ IVD™, R & D systems, MN, USA).
Table 1. Biochemical and hematological parameters of chronic kidney disease patients determined before, and at 10 and 20 weeks of EPO treatment (group 1), compared with patients (group 2) not treated with EPO and followed for 20 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Before</th>
<th>10 weeks</th>
<th>20 weeks</th>
<th>Group 2 Before</th>
<th>20 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>218.4 ± 9.7</td>
<td>205.7 ± 11.2</td>
<td>211.4 ± 11.8</td>
<td>196.7 ± 18.2</td>
<td>184.4 ± 12.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>201.3 ± 25.5</td>
<td>200.5 ± 31.9</td>
<td>227.9 ± 37.5</td>
<td>193.1 ± 32.2</td>
<td>158.4 ± 21.5</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>42.1 ± 0.3</td>
<td>39 ± 0.4</td>
<td>29.1 ± 1.0*</td>
<td>3 ± 0.3</td>
<td>3.8 ± 0.4*</td>
</tr>
<tr>
<td>Range</td>
<td>2.3–8.6</td>
<td>2.5–7.4</td>
<td>2.1–6.9</td>
<td>2.4–7.3</td>
<td>2.6–6.8</td>
</tr>
<tr>
<td>Calculated GFR</td>
<td>14.7 ± 1.2</td>
<td>14.8 ± 1.1</td>
<td>14.1 ± 1.1</td>
<td>14.4 ± 1.3</td>
<td>11.1 ± 1.0*</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.6 ± 0.1</td>
<td>10.9 ± 0.3</td>
<td>11.5 ± 0.4</td>
<td>10.7 ± 0.2</td>
<td>9.4 ± 0.2*</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.1 ± 0.6</td>
<td>32 ± 1.1</td>
<td>34.3 ± 1.2*</td>
<td>31.2 ± 0.9</td>
<td>28.5 ± 0.5*</td>
</tr>
<tr>
<td>Transferrin sat. (%)</td>
<td>18.1 ± 1.6</td>
<td>16.0 ± 0.9</td>
<td>19.9 ± 1.7</td>
<td>16.6 ± 3.2</td>
<td>12.6 ± 3.2</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>98 ± 14.3</td>
<td>66 ± 9.2</td>
<td>63 ± 7.9</td>
<td>65.8 ± 17</td>
<td>48.5 ± 5.3</td>
</tr>
<tr>
<td>WBC (x 10^3/L)</td>
<td>9 ± 0.5</td>
<td>7 ± 0.5</td>
<td>7.6 ± 0.5*</td>
<td>8.4 ± 0.2</td>
<td>8.8 ± 0.4</td>
</tr>
<tr>
<td>PMNLs (x 10^9/L)</td>
<td>6.4 ± 0.3</td>
<td>5.3 ± 0.3*</td>
<td>5.2 ± 0.4*</td>
<td>5.7 ± 0.1</td>
<td>6.1 ± 0.4</td>
</tr>
<tr>
<td>ALP (U/ml)</td>
<td>239 ± 17</td>
<td>192.9 ± 18.4</td>
<td>131.1 ± 12.7*</td>
<td>229.1 ± 45.6</td>
<td>268.7 ± 60.2*</td>
</tr>
<tr>
<td>EPO-R (%)**</td>
<td>5.27 ± 1.3</td>
<td>4.00 ± 0.3</td>
<td>2.16 ± 0.5*</td>
<td>4.75 ± 1.07</td>
<td>4.55 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* P < 0.05 in group 1 vs. values before EPO treatment, in group 2 vs. time 0.

** The percentage of PMNLs expressing EPO receptors.

Detection of PMNLs expressing EPO-R

EPO-R expression on PMNLs from all kidney disease patients before and after EPO treatment and from healthy control PMNLs was detected by flow cytometry using fluorescent monoclonal anti-human EPO-R antibodies (R&D systems). The non-specific mouse anti-immunoglobulin G fluorescence was subtracted from EPO-R fluorescence, as previously described [6]. The results are presented as percent of PMNLs expressing EPO-R (%).

Statistical analysis

Data were expressed as means ± SEM. Differences between the study parameters were compared by paired or unpaired student t-test, or by one-way analysis of variance, according to the experimental requirements. The correlation between different study parameters was performed by linear and non-linear regression analysis using Spearman and Pearson correlation coefficients. P < 0.05 was considered significant.

Results

Effect of EPO on biochemical parameters and GFR

The EPO-treated kidney patients and the non-EPO treated patients showed non-significant differences in the levels of blood glucose, cholesterol, triglycerides and albumin during the study [Table 1]. Hemoglobin and hematocrit levels increased in the EPO-treated group, reaching significance for hematocrit [Table 1], while in group 2 both hemoglobin and hematocrit demonstrated a significant decrease. A stable GFR was observed in the EPO-treated group 1, compared to a significant increase in serum creatinine and a decrease in GFR in the absence of EPO in group 2 [Table 1].

The individual GFR profiles of group 1 are depicted in Figure 1 (left panel). The calculated GFR in these EPO-treated patients is shown 10 weeks before (as recovered from the patients' files) and after 10 and 20 weeks of treatment with the hormone. A significant (P = 0.001) deterioration in the average GFR from 17.4 ± 1.3 to 14.7 ± 1.2 ml/min/1.73 m² was demonstrated during 10 weeks prior to EPO treatment, similar to the rate of deterioration observed in group 2. However, during the two periods of 10 weeks of EPO treatment in group 1, the GFR decline was retarded. It showed similar calculated GFR values of 14.7 ± 1.2, 14.8 ± 1.2 and 14.1 ± 1.1 ml/min/1.73 m² at 0, 10 and 20 weeks of EPO treatment, respectively.

PMNL priming – in vivo

- Rate of superoxide release from separated PMNLs of kidney patients. The rate of superoxide release from PMA-stimulated PMNLs was monitored in group 1 after 10 and 20 weeks of EPO treatment and in group 2 after 20 weeks without EPO. Both 10 and 20 weeks of EPO treatment in kidney patients induced a significant reduction in the rate of superoxide release from PMA-stimulated PMNLs, with a significant 40% further reduction between 10 and 20 weeks [Figure 2]. The rate of superoxide release after 20 weeks of EPO treatment was similar to that of PMNLs separated from healthy control subjects (11 ± 1.2 nmoles/10⁶ cells/10 min). In PMNLs separated from patients not treated with EPO, the rate of superoxide release during 20 weeks was not attenuated and
stayed significantly elevated compared to patients after 20 weeks of EPO treatment [Figure 2]. No correlation could be found between the rates of superoxide release from separated PMNLs and the hemoglobin levels following 10 weeks (r = 0.5, P = 0.1) or 20 weeks (r = 0.17, P = 0.6) of EPO treatment. Nevertheless, the rate of superoxide release from separated PMNLs from all participants, without or before EPO treatment, negatively correlated with GFR (r = -0.315, P = 0.002, n=58). This correlation is similar to the one previously reported [3].

- **WBC and PMNL counts.** EPO treatment caused attenuation of the increase in WBC and PMNL counts, while without EPO treatment the counts tended to increase [Table 1]. EPO treatment caused a significant decrease in WBC and PMNL counts in kidney patients, compared to the pretreatment values, reaching the cell counts of healthy controls (WBC 6.7 ± 0.2 10^9/L; PMNLs 3.9 ± 0.2) [Table 1].

- **Alkaline phosphatase.** ALP activity measured after 20 weeks of EPO treatment decreased significantly compared to its level before EPO treatment, reaching healthy control levels (141 ± 11 U/ml). Without EPO treatment ALP activity increased [Table 1]. A linear regression analysis revealed strong positive correlations between ALP activity and the rate of superoxide release from separated PMNLs (r = 0.37, P = 0.02), and between ALP activity and PMNL counts (r = 0.4, P = 0.0049).

### The ex vivo effects of EPO on PMNL functions

- **PMNL priming.** When PMNLs from untreated kidney patients were incubated ex vivo with increasing concentrations of EPO, a dose-dependent reduction in the rate of superoxide release was detected already at 5 U/ml, a concentration within the therapeutic range, reaching significance at 10 U/ml (P < 0.05) [Figure 3A].

- **PMNL survival.** When EPO was added to PMNLs isolated from non-EPO-treated patients, already 5 U/ml of EPO significantly promoted PMNL survival.
improvement in PMNL survival by ex vivo results, where r...

In a longitudinal follow-up, PMNLs from r by EPO reduction in peripheral PMNL counts: less cell death and a r by EPO for 20 weeks, a complete correction of the PMNL priming in inflammation directly related to the severity of kidney function accompanied by PMNL priming and increased low grade systemic treatment.

EPO-R is down-regulated by increased s-EPO levels, namely EPO should be noted that the increased percentage of cells expressing levels and are probably mediated by the EPO-R on PMNLs. It disease patients are not related to the correction in hemoglobin...suggests a down-regulation of EPO-R by increasing endogenous EPO (s-EPO) levels. The percentage of kidney disease PMNLs expressing EPO-R before EPO treatment was relatively high compared to healthy control subjects (5.5 ± 1.3 vs. 2.6 ± 0.65%, respectively). After 20 weeks of hormone administration, a twofold decrease in the percentage of EPO-R-expressing cells was observed (Table 1), similar to its level in healthy controls.

EPO regulation of PMNLs is distinct from its role in erythropoiesis, as there was no significant correlation between PMNL EPO-R and blood hemoglobin levels (r = 0.3, P = 0.13, n=58). Nevertheless, PMNLs expressing EPO-R positively correlated with the rate of superoxide release from these cells (r = 0.4, P = 0.0004), the higher the priming state the more PMNLs carrying EPO-R are present. In addition, the percentage of PMNLs expressing EPO-R negatively correlated with GFR (r = -0.32, P < 0.05, n=58); the lower the GFR the higher the percentage of PMNLs expressing EPO-R.

**Discussion**

This study adds a new renal protection effect of EPO in patients with chronic kidney disease, via attenuation of PMNL priming and related inflammation: EPO attenuated PMNL priming and PMNL mediated inflammation concomitantly with retarding the decline of estimated GFR, EPO modulated PMNL priming both α α and in vivo. In a longitudinal follow-up, PMNLs from kidney disease patients treated with EPO showed a reduced rate of superoxide release, similar to the α α results, where EPO inhibited the rate of superoxide release from separated PMNLs in a dose-dependent manner. EPO caused a decrease in WBC and PMNL counts, reflecting a decrease in systemic low grade inflammation. Promotion of PMNL survival α α by EPO suggests a new property of the hormone as a viable anti-inflammatory factor. These non-erythropoietic effects of EPO in kidney disease patients are not related to the correction in hemoglobin levels and are probably mediated by the EPO-R on PMNLs. It should be noted that the increased percentage of cells expressing EPO-R is down-regulated by increased s-EPO levels, namely EPO treatment.

We have recently shown that chronic kidney disease is accompanied by PMNL priming and increased low grade systemic inflammation directly related to the severity of kidney function [3]. The present study supports these findings in another group of kidney disease patients. When these patients were treated with EPO for 20 weeks, a complete correction of the PMNL priming state to healthy control levels occurred. EPO treatment attenuated the rate of superoxide release to levels observed in healthy control subjects, while during 20 weeks in a similar group of patients but not receiving EPO, the priming state of PMNLs was unchanged or even worsened. It must be mentioned that the correction of PMNL priming to healthy control levels by EPO was not achieved in patients on maintenance hemodialysis treated with EPO. In these chronic hemodialysis patients the amelioration in PMNL priming, although pronounced, did not reach normal levels [4]. The lowering of superoxide anion release to normal levels by EPO treatment renders antioxidative properties to the hormone. Hence, it is easy to envisage that in the face of lower antioxidant levels in kidney disease patients [11] systemic oxidative stress will increase.

Low grade PMNL-related inflammation, reflected by an increase in WBC and PMNL counts, was shown by us in many clinical states: in early pregnancy [12], in cigarette smokers [13], in type 2 diabetic patients [14], in hyperlipidemic patients [15], in essential hypertensive patients [8], at all stages of uremia [3], and in patients on hemodialysis [4] or on continuous ambulatory peritoneal dialysis [5], and is also supported here by another group of kidney disease patients before renal replacement therapy. In addition, EPO treatment ameliorated the PMNL-related low grade systemic inflammation as reflected by the reduction in WBC and PMNL counts; whereas during 20 weeks without EPO treatment the PMNL counts did not change and even increased slightly. The α α improvement in PMNL survival by EPO lowering cell disintegration provides an explanation for the α α reduction in peripheral PMNL counts: less cell death and a reduced release of inflammatory and chemotactic mediators from PMNLs, decelerating the inflammatory vicious cycle and ending in less PMNL recruitment. This anti-inflammatory characteristic of EPO was also shown for hemodialysis and continuous ambulatory peritoneal dialysis patients in our previous studies [4,5].

PMNL-mediated inflammation resulting from PMNL activation and degranulation is also suggested by elevated serum ALP activity. Increased ALP activity in kidney disease patients in the absence of liver disease usually reflects increased secondary hyperparathyroidism and high bone turnover. Although PMNLs are not usually identified as the source of increased serum ALP activity, they can still serve as a source of neutrophil alkaline phosphatase [10]. We suggest that the increased serum ALP may reflect PMNL degranulation and priming, as already reported for hypertensive patients, for Dahl hypertensive rats and in early pregnancy [8,9,12]. This increased serum ALP approaches normal levels after 20 weeks of EPO treatment in kidney disease patients. The correction of ALP levels, together with the significant correlation shown here between serum ALP and PMNL priming and counts, strengthen the notion that the primed PMNLs contribute to the increased serum ALP levels. In the absence of liver disease, the decrease in ALP to normal levels together with the preservation of GFR by EPO treatment plausibly rules out the bone origin of this enzyme and emphasizes the beneficial non-erythropoietic effects of EPO.

The percentage of kidney disease PMNLs expressing EPO-R...
Erythropoietin, PMNL and Kidney Function

2005;45:39–47.

A recent study reported a decrease in renal function after 12 months follow-up, which was greater in untreated patients than in those treated with EPO. This was due to the anemia that developed in this group, which ethically compelled us to initiate EPO treatment. Yet, the statistically significant effect of EPO on GFR, despite the small sample size, emphasizes the importance of our findings. This study focuses on PMNL-related inflammation, hence only WBC and PMNL counts and serum ALP levels were used as markers of low grade inflammation.

Despite these limitations, we believe that our findings are important and further support the previously reported beneficial non-erythropoietic characteristics of epoetin-alpha. Moreover, since we show a possible retardation in the rate of progression of chronic kidney disease, even in its advanced stages, it is tempting to recommend early EPO replacement therapy, as recommended by the Dialysis Outcomes Quality Initiative, when GFR is above 60 ml/min. The combined non-erythropoietic effects of EPO, the local renoprotection exhibited through EPO-R on renal cells, and the interaction with EPO-R on PMNLs, decreasing systemic oxidative stress and inflammation, may retard the rate of deterioration of renal functions and postpone the initiation of renal replacement therapy. Obviously, additional large-scale studies with control groups are warranted.

References


Acknowledgment. This work was partially supported by a grant from by the R.W Johnson Pharmaceutical Research Institute, a division of Ortho-McNeil Pharmaceutical, Inc. The statistical help of Mrs. Orly Yakir is gratefully acknowledged.
Capsule

Regenerating heads or tails

Planarians – tubular flatworms – can regenerate all of their body parts and entire organ systems after amputation. However, the mechanism by which the animal “knows” how to generate a head after head removal or a tail after tail removal, a property called regeneration polarity, is unknown. Gurley et al. (Science 2008;319:323) and Petersen and Reddien (p. 327) found that a conserved factor within the Wnt signaling pathway is used to distinguish head from tail. Decreased Wnt signaling through beta-catenin causes the regeneration of heads, whereas activation of Wnt signaling induces tails.

Eitan Israeli

Capsule

Goldfish with Parkinson’s disease

Technion researchers together with the National Institutes of Health in the U.S. have built a model that simulates Parkinson’s disease (PD) in goldfish. PD has been modeled in humans, lower primates, and to a lesser extent also in other vertebrates using the neurotoxin MPTP. The model goldfish, developed 15 years ago by Prof. Moussa Youdim from the Technion, is a system used to search for anti-PD drugs. Youdim himself used it to develop Teva’s anti-Parkinson drug rasagiline. The simple and inexpensive procedure of injecting MPTP into goldfish takes 14 to 30 days. The single injection causes injury in early atherosclerosis and renovascular disease. Circulation 2002;106:1165–71.


Correspondence: Dr. B. Kristal, Head, Dept. of Nephrology and Hypertension, Western Galilee Hospital, Nahariya 22100, Israel. Phone: (972-4) 910-7603/4; Fax: (972-4) 910-7482, email: batya.kristal@naharia.health.gov.il