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Letter to the Editor

Is There a Role of Erythropoietin Treatment in Systemic Disorders with Renal Involvement?

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Dear Editor,

The production of erythropoietin (EPO) in human renal peritubular fibroblasts is regulated by arterial oxygen tension via a mechanism that is not fully understood but is known to involve oxygen-dependent conformational changes of the hem molecule [1]. The damage of the EPO-producing apparatus that occurs in renal disease lead to inadequate EPO production followed by a fall in hematocrit, which is commonly known as renal anemia [1-3]. On the other hand, there is also another mechanism of anemia in chronic diseases that is inhibition of EPO axis. Hence, the anemia in chronic diseases combined with the inadequate EPO response has been observed in a variety of disorders, such as rheumatoid arthritis, tumors, inflammatory bowel disease and acquired immunodeficiency syndrome [3-5]. Occasional re-ports have been published favoring substitution with the recombinant EPO as a therapy for anemia in SLE, while the others report EPO resistance in patients with high disease activity [6,7]. There are only two reports on EPO treatment in chronic vasculitis [8, 9].

In this letter, we present our experience with EPO treatment in 4 patients with systemic diseases, 3 SLE patients and one with Wegener's granulomatosis, with severe anemia not corresponding with the degree of renal failure.

Case 1

63-year old male patient was admitted at Department of Nephrology in November, 2008 because of acute oligoanuria and bilateral lung infiltration. Severe anemia was also present at admission (Hb 67g/l, RBC count 2100.000/ mm3, Hct 0,21). Renal biopsy was performed and histopathological examinations presented diffuse proliferative glomerulonephritis with crescents, with disruption of Bowman's membrane and fibrin exudation. Positive ANCA and pulmonary granulomatosis confirmed the diagnosis of Wegener's granulomatosis. The patient was treated with plasma-exchanges, i.v. steroids and cyclophosphamide, besides the dialysis and blood transfusions. After complete recovery of the pulmonary changes and partial improvement of the renal function (serum urea level 27 mmol/l, serum creatinine level 365 μmol/l) the patient started out-patient follow-up and treatment.

Maintenance therapy consisted of low-dose steroids. In this stable phase of the underlying disease, erythropoietin treatment (4000 IU/weekly) was started on January 2009 because of the severe anemia (Hb 71g/l, RBC 2600.000/mm3, Hct 0,22). Anemia was present regardless of the further improvement of renal function (serum urea levels 26,7 mmol/l and serum creatinine of 286 μmol/l). Complete recovery of anemia was achieved after 6 months of treatment, along with the improvement in the renal function (serum urea 8,4 mmol/l, and serum creatinine 153μmol/l).

Case 2

46-year-old female patient, diagnosed as SLE and lupus nephritis (without renal biopsy) at the Department of Rheumatology, was transferred to out-patient service at Department of Nephrology in January 2009 because of development of initial phase of chronic renal failure. She was already put on maintenance steroid and mycophenolate mofetil treatment, being at 4 months after the last relapse of the disease. EPO treatment was started in April 2009, because of severe anemia (Hb 81g/l, RBC count 2800.000/mm3, Hct 0,28), 4000 IU/weekly. Serum urea levels at start of the follow-up were 28,6 mmol/l and serum creatinine 271 μmol/l. After 6 months the patient presented with complete recovery from anemia and improved renal function with serum urea level of 16,2 mmol/l and serum creatinine of 152 μmol/l. Of note, in the mean time, mycophenolate mofetil was excluded from its maintenance therapy.

Case 3

21-year-old female patient was documented as lupus nephritis class IV at Department of Nephrology in 2003. Her renal function in that moment was normal, severe nephrotic syndrome was present with proteinuria 8g/ daily. The patient started out-patient treatment with steroids (i.v., orally) and mycophenolate mofetil and achieved satisfactorily remission of the nephrotic syndrome. She was left on maintenance steroid treatment during 2007, and last control examinations before the relapse of the disease made in January 2008 were: se-

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rum levels of urea 2,8 mmol/l, creatinine 45 μmol/l, plasma proteins level 72g/l, and daily protein loss of 0,37g/l (0,59g/d). She stopped the follow-up and steroid treatment, and the relapse of the disease occurred in August 2008. Severe nephrotic syndrome was the first clinical sign (daily protein loss of 11,93g), followed by anuria with rapid deterioration of the renal function and severe anemia. Incomplete remission was achieved with steroids i.v., orally, cyclophosphamide i.v. and plasma exchanges. Hemodialysis and blood transfusions were supportive treatment. After appearance of diuresis and cessation of dialysis, once she stabilised in October 2008, she started again out-patient treatment with serum urea level of 26,3 mmol/l and serum creatinine of 238 μmol/l. Nephrotic syndrome was still present (proteinuria 6,95g/l), as well as severe anemia (Hb 67g/l, RBC count 2300.000, Hct 0,19). The maintenance therapy included steroids orally and mycophenolate mofetil and EPO 4000 IU/weekly was also included. After 6 months of treatment she presented complete recovery of anemia, along with the improved renal function (serum urea levels of 6,7 mmol/l, creatinine 115 μmol/l, and proteinuria of 2,7 g/daily).

Case 4

20-year-old male patient, previously diagnosed and treated as SLE at the Department of Rheumatology, was admitted at Department of Nephrology in January 2008 because of the development of initial renal failure. Serum urea level was 28,4 mmol/l and serum creatinine 124 μmol/l. Anemia was also present, with Hb 98 g/l, RBC count 3000.000/mm3 and Hct 0,27, as well as nephrotic syndrome with daily protein loss of 6,4g. Renal biopsy revealed lupus nephritis class IV+V. The patient started out-patient treatment with steroids orally and mycophenolate mofetil. Control examinations in April 2008 presented further worsening of the renal failure (serum urea 31,5 mmol/l, serum creatinine 212 μmol/l) and anemia (Hb 81gl, RBC count 2800.000, Hct 0,24). In this stable phase, treatment with EPO 4000/IU weekly was added to the maintenance therapy with steroids and mycophenolate mofetil. After 6 months of follow-up a complete recovery of anemia was noted. Significant improvement of renal failure was also observed with serum urea of 8,9 mmol/l, and serum creatinine of 99 μmol/l. Proteinuria decreased to non-nephrotic ranges (0,48 g/l, 0,96 g/daily). The patient is still in stable phase-se of the disease, maintained on low doses of steroids and mycophenolate mofetil orally.

In conclusion, clinicians are often faced with a patient with SLE who is anemic. Although it was initially suspected that anemia in SLE was mainly result of the damage of erythrocytes, evidence to date indicates that anemia pathogenesis may be immune or non-immune in nature. Anemia of chronic diseases, iron deficiency anemia, autoimmune anemia, anemia of chronic renal failure and cyclophosphamide anemia are the most common causes [1,2,10]. Recent studies have shown that resistance to EPO action in SLE can be attributed also to anti-EPO antibodies [3-5]. Our patients were presented with severe form of lupus nephritis, but the therapy with EPO was initiated in the phase of maintenance treatment. All of them were in the phase of renal failure, so anemic syndrome could be associated with two disorders: either autoimmune and/or associated with the chronic disease. Interestingly, there was no correlation with the degree of renal failure and the degree of anemia at start of the follow-up. Hence, as a conclusion concerning to EPO treatment in SLE, with respect to the therapeutic administration of EPO, we should postulate that: [1] the anemia in SLE is characterized by an inadequate EPO production due to the renal disease; [2] the anemia in SLE, like other types of anemia such as infection- or inflammation-associated anemia, may be proven as EPO resistant; and [3] antibodies may be present leading to the underestimation of EPO levels, especially in the active phase of the disease. In addition, the possibility of renal function improvement in parallel to the anemia improvement could not be completely excluded.

On the other hand, data on EPO treatment in chronic vasculitis [8,9] including Wegener's granulomatosis are obscure, and we had only one case successfully treated. Hence, we could not draw any valid conclusion and at least future observational reports should be awaited.

Conflict of interest statement. None declared.

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