Erythropoiesis-stimulating agent slows the progression of chronic kidney disease: a possibility of a direct action of erythropoietin

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ABSTRACT
Background Controversy exists regarding the renoprotective effect of erythropoiesis-stimulating agent (ESA) in progressive chronic kidney disease (CKD) with renal anemia. In this study, we examined whether ESA therapy has a renoprotective effect in progressive CKD.

Methods The subjects in this retrospective observational study were 68 non-dialysis dependent CKD patients with renal anemia. We compared the progression rate (PR), defined by the slope of the linear regression line of estimated glomerular filtration rate, measured during 6 months just before and after the start of ESA therapy. We also investigated the factors affecting renoprotective efficacy of ESA therapy against the progression of CKD.

Results Median (interquartile range) PR decreased significantly from 6.2 (3.7–12.7) to 4.0 (0.3 to 7.3) mL/min/1.73 m²/year after the start of ESA therapy. Blood pressure levels and rate of medication with renin-angiotensin system inhibitors were comparable between the two periods. Next, we investigated the factors affecting renoprotective efficacy of ESA therapy against the progression of CKD. Thirty patients were good renal responders, defined as those with the ratio of post-/pre-PR of ≥0.5 and the difference of pre- minus post-PR ≥5.0 mL/min/1.73 m²/year, and 38 patients were poor renal responders who did not meet the definition of good renal responders. Multivariable logistic regression analysis showed that weekly ESA dose, but not increase in hemoglobin level, was a significant and independent determinant of the renoprotective effect of ESA.

Conclusion ESA therapy slows the progression of CKD and part of the effect might be attributed to the direct renoprotective action of ESA.

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Introduction
Chronic kidney disease (CKD) is characterized by progressive kidney damage and impaired kidney function. When CKD progresses to end-stage renal disease (ESRD), chronic dialysis or a kidney transplant is required to sustain life. Anemia is a common complication of CKD that may begin in the early stages of the disease and becomes more common and severe with deterioration of renal function, and has been proposed as one of the major factors that contribute to the progression of CKD.1,2 Erythropoiesis-stimulating agent (ESA) has been reported to have an organ-protective effect in several organs such as kidney, heart, and brain, through the improvement of anemia and/or its own direct cytoprotective action.3 With regard to the renal system, several clinical trials have demonstrated the inhibitory effect of ESA against the progression of CKD. For example, Kuriyama et al.4 reported a renoprotective effect of ESA in patients with predialysis CKD, and Gouva et al.5 also showed in a randomized controlled trial (RCT) that treatment of anemia in CKD patients could slow the decline in renal function in 88 non-diabetic predialysis CKD patients. Similarly in diabetic CKD, post-hoc analysis of the RENAAL study data6 demonstrated that a higher hemoglobin level was associated with a slower rate of progression of diabetic nephropathy.

On the other hand, two large studies, the CREATE study7 and CHOIR study,8 did not detect any renoprotective effects for anemia correction to the levels of healthy individuals. Subsequently, more strong evidence that endorses the conclusions of these two studies was published from the TREAT study.9 The study confirmed that patients treated with active ESA required fewer blood transfusions and suffered less fatigue, however, the same treatment failed to reduce mortality, cardiovascular morbidity, and halt progression to ESRD. Whereas in
Japan, Tsubakihara et al." randomly divided 321 patients with CKD not on dialysis with serum creatinine (sCr) > 2 mg/dL and hemoglobin <10 g/dL into two hemoglobin target groups; 11.0–13.0 g/dL by treatment with darbepoetin alfa, and 9.0–11.0 g/dL with epoetin alfa, and compared the composite renal endpoint defined as initiation of renal replacement therapy, doubling of sCr, renal transplantation, or death. The renal survival rate estimated by Kaplan–Meier tended to be higher in the high hemoglobin target arm, albeit insignificantly.

The present study tested the hypothesis that ESA therapy ameliorates the progression of CKD. To test this hypothesis, we compared the progression rate (PR) of CKD before and after ESA therapy. The results showed a renoprotective effect of ESA in patients with progressive CKD.

Methods

Recruitment of patients

We recruited 68 Japanese patients with progressive CKD and renal anemia in whom administration of ESA [subcutaneous injection of epoetin α to 38 patients (56%) and epoetin β to 30 patients (44%)] was started between January 2005 and October 2008 and whose clinical data including sCr and hemoglobin concentration were available at least once bimonthly for 6 months just before and the subsequent 6 months after the start of ESA therapy.

The indication to start ESA therapy in this study was when the hemoglobin level was less than 10 g/dL in several test results following a diagnosis of renal anemia. Target hemoglobin level was 10 g/dL or higher, which is lower than the target hemoglobin level (11 g/dL or higher) recommended by Japanese Society for Dialysis Therapy guidelines for renal anemia. Target hemoglobin level was 10 g/dL or higher, which is lower than the target hemoglobin level (11 g/dL or higher) recommended by Japanese Society for Dialysis Therapy guidelines for renal anemia in CKD, because this guideline had not been published when the recruited patients received ESA therapy.

Tables 1 and 2 list the clinical profiles and various parameters measured at the initiation of ESA therapy. Both sexes were equally recruited and patients with diabetic nephropathy as an original disease formed 25% of the recruited patients. The mean (SD) age was 62 (15) years and most (90%) patients were being treated with renin-angiotensin system (RAS) inhibitor. The mean (SD) sCr and hemoglobin were 3.9 (1.7) mg/dL and 8.9 (0.8) g/dL, respectively, and the median (interquartile range; IQR) estimated glomerular filtration ratio (eGFR) was 12.6 (9.2–18.2) mL/min/1.73 m², indicating that the subjects in the present study were in a relatively advanced state of CKD and renal anemia.

Study design and definition of CKD progression rate

We compared the PR measured during 6 months just before and after the start of ESA therapy. The sCr level was measured in all samples by the enzymatic method. The eGFR was calculated using the following equation:

\[ eGFR (\text{mL/min/1.73m}^2) = 194 \times S \text{Cr}^{-1.094} \times A e^{-0.287} (0.739, \text{if female}) \]

PR (mL/min/1.73 m²/year) was defined as the rate of deterioration of eGFR. Pre-PR and post-PR were calculated from the slope of the regression line during 6 months just before and after the start of ESA therapy, respectively. We also investigated the factors affecting renoprotective efficacy of ESA therapy against the progression of CKD.

The study protocol was approved by the local ethics committee of Kyushu University Hospital (No. 25-300)

| Table 1. Clinical profile at the start of ESA therapy (N = 68). |
|-----------------|-----------------|
| Male/female, n  | 34/34            |
| Age, years      | 62 ± 15         |
| Original kidney disease (DM/non-DM), n | 17/51 |
| Chronic glomerulonephritis, n (%) | 23 (34) |
| Diabetic nephropathy, n (%) | 17 (25) |
| Nephrosclerosis, n (%) | 13 (19) |
| Polycystic kidney disease, n (%) | 3 (4) |
| Others, n (%)   | 12 (18)         |
| Blood pressure  |                 |
| Systolic blood pressure, mmHg | 137 ± 16 |
| Diastolic blood pressure, mmHg | 72 ± 11 |
| Treatment with RAS inhibitors, n (%) | 61 (90) |
| Treatment with ARB, n (%) | 50 (74) |
| Treatment with ACE inhibitor, n (%) | 13 (19) |
| Data are mean ± SD or number (percentage) of patients. ESA, erythropoiesis-stimulating agent; DM, diabetes mellitus; RAS, renin-angiotensin system; ARB, angiotensin II receptor blocker; ACE, angiotensin I converting enzyme. |

| Table 2. Clinical parameters at the start of ESA therapy (N = 68). |
|-----------------|-----------------|
| Total protein, g/dL | 6.7 ± 0.8 |
| Albumin, g/dL    | 3.9 (3.4–4.0) |
| Blood urea nitrogen, mg/dL | 57 ± 19 |
| Serum creatinine, mg/dL | 3.7 (2.6–4.9) |
| Uric acid, mg/dL  | 7.3 ± 1.8 |
| Sodium, mEq/L    | 141 ± 2 |
| Potassium, mEq/L  | 5.0 ± 0.7 |
| Chloride, mEq/L   | 110 ± 12 |
| Calcium, mg/dL    | 8.5 ± 0.8 |
| Phosphate, mg/dL  | 4.3 (3.8–4.9) |
| Total cholesterol, mg/dL | 174 (142–194) |
| Triglycerides, mg/dL | 112 (82–166) |
| Hemoglobin, g/dL  | 8.9 ± 0.8 |
| Hematocrit (%)    | 27.7 ± 2.5 |
| C-reactive protein, mg/dL | 0.11 (0.05–0.48) |
| Up/Ucr, g/gCr     | 2.2 (0.8–4.3) |
| eGFR, mL/min/1.73 m² | 12.6 (9.2–18.2) |

Data are mean ± SD or median (interquartile range). ESA, erythropoiesis-stimulating agent; Up/Ucr, urinary protein/creatinine ratio; eGFR, estimated glomerular filtration rate.
and registered in the clinical trial registry (UMIN000013311). This study was performed according to the Ethics of Clinical Research (Declaration of Helsinki).

**Evaluation of factors associated with the renoprotective response to ESA therapy**

The renoprotective efficacy of ESA therapy was determined from the extent of PR change. Good renal responders represented patients with both pre-post difference (pre-PR minus post-PR) larger than 5 mL/min/1.73 m²/year and post/pre ratio of PR (post-PR/pre-RP) smaller than 0.5. The cutoff values represented the median values of pre-post difference and post/pre ratio of PR. The poor renal responders were defined as those who did not meet the definition of good renal responders.

**Statistical analysis**

Estimated GFR and PR between the baseline (before ESA) and after ESA therapy were compared by Wilcoxon’s signed rank test. Between good and poor renal responders, continuous variables were compared using Student’s t-test or the Mann–Whitney U test and categorical variables using the chi-square test or Fisher’s exact test according to the normality of the distribution of the data. A multivariable logistic regression analysis was applied to determine the factors associated with the renoprotective efficacy of ESA therapy. The proportion of good renal responders in the groups divided according to quartiles of the dose of ESA was compared using the Cochran–Armitage test. A Kaplan–Meier analysis with log-rank test was used to compare renal survival between the good and poor renal responders. Data are expressed as mean ± SD, median (IQR), or number (%). A p values less than 0.05 denoted the presence of a statistically significant difference.

**Results**

**ESA therapy slows the PR of CKD**

The median (IQR) ESA dose administered during 6 months was 2330 (1690–3190) U/week [40.4 (29.1–52.7) U/kg/week]. The median (IQR) eGFR decreased over time, being 16.2 (11.9–23.8), 12.6 (9.2–18.2), and 10.0 (6.8–14.4) before 6 months, at the start, and after 6 months of ESA therapy, respectively (Figure 1). The median (IQR) PR during 6 months decreased significantly from 6.2 (3.7–12.7) before ESA therapy to 4.0 (–0.3 to 7.3) mL/min/1.73 m²/year after ESA therapy (p < 0.0001, Figure 2). On the other hand, the mean blood pressure (137/72 vs. 138/71 mmHg) and percentage of patients treated with renin-angiotensin inhibitors (78% vs. 81%) were comparable between the two periods.

**ESA dose as an independent factor associated with the renoprotective effect of ESA**

The weekly dose of ESA was significantly larger in the good renal responders than the poor renal responders.
There were also significant differences in diastolic blood pressure, sCr, eGFR, and pre-PR between the two groups (Supplementary Tables S1 and S2). However, there was no difference in the amount of change in hemoglobin level between the high and poor renal responders (Supplementary Table S2). A multivariable logistic regression analysis identified the “weekly dose of ESA” as a significant and independent determinant of the renoprotective efficacy of ESA therapy, and the odds ratio for the effect of every 10 units/kg/week increase in ESA dose was 1.39 (Table 3).

Based on these results, the subjects were divided into quartile groups according to weekly dose of ESA (<29.1; 29.1–40.4; 40.4–52.7; >52.7 units/kg/week). The proportion of the good renal responders increased in accordance with higher weekly dose of ESA (Figure 3, p = 0.002).

**Outcome**

During the follow-up period (48.4 ± 16.7 months), 7 (10.3%) patients died and 2 (2.9%) patients developed stroke (annual incidences of death and stroke: 2.6% and 0.7%, respectively). Malignancies were detected in 7 (10.3%) patients, 4 (5.9%) of whom developed hepatocellular carcinoma and the remaining 3 (4.4%) had colonic cancer. There were no significant differences in these outcomes between good and poor renal responders, except for modest significant difference in development of colonic cancer between them, although the follow-up periods were significantly longer in good renal responders than in poor renal responders (Supplementary Table S3).

**Discussion**

The present study demonstrated a renoprotective effect of ESA therapy in patients with progressive CKD and the results suggested that the efficacy of ESA was due to the direct effect of ESA in addition to a indirect effect through improvement of anemia.

In CKD, anemia decreases the tissue oxygen partial pressure in the renal interstitium and accelerates interstitial damage due to “hypoxia”, which contributes to the progression of CKD as a final common pathway. Improvement of anemia by ESA therapy is associated with increased oxygen supply to the renal interstitium due to an increase in the oxygenized hemoglobin content and cardiac function, which in turn slows down the progression of CKD. In the point of view of this mechanism, a previous study reported by Kuriyama et al. represented the renoprotective effect due to improvement of anemia. A post-hoc analysis of the previously reported RCT by Tsubakihara et al. also demonstrated that achieving a higher target hemoglobin level with ESA is associated with a greater renoprotective effect in patients with stage 5 CKD. Likewise, in our study, mean hemoglobin level is significantly increased from 8.9 to 9.4 g/dL after 6 month of ESA therapy, thus, it is considered that one mechanism of renoprotective effect must be attributed to improvement of anemia.

In addition to the indirect action through improvement of anemia, the renoprotective effect of ESA was suggested due to the direct organ-protective property of ESA in the present study. Various studies have shown that ESA has an organ-protective effect independent of

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**Table 3. Multivariable logistic regression analysis for good renal responder to ESA therapy**

| Outcome | Odds ratio | 95% CI | p |
|---------|------------|--------|---|
| Weekly dose of ESA (10 U/kg/week) | 1.39 | 1.05–1.97 | 0.019 |
| Diastolic blood pressure (mmHg) | 0.95 | 0.89–1.02 | 0.156 |
| Hemoglobin (g/dL) | 0.96 | 0.90–1.02 | 0.923 |
| C-reactive protein (mg/dL) | 1.75 | 0.90–4.45 | 0.113 |
| Up/Ucr (g/gCr) | 0.89 | 0.63–1.21 | 0.149 |
| eGFR (mL/min/1.73 m²) | 1.11 | 0.96–1.30 | 0.149 |
| Pre-PR (ml/min/1.73 m²/year) | 1.12 | 1.00–1.30 | 0.052 |

*Good renal responder to ESA therapy was defined as the ratio of post-/pre-PR of <0.5 and the difference of pre- minus post-PR >5.0 mL/min/1.73 m²/year. ESA, erythropoiesis-stimulating agent; CI, confidential interval; Up/Ucr, urinary protein/creatinine ratio; eGFR, estimated glomerular filtration rate; pre-PR, progression rate during 6 months before ESA therapy.*
anemia correction.\textsuperscript{14} Animal experiments have demonstrated recently that other types of erythropoietin (EPO) without erythropoiesis-stimulating activity, such as asialo-EPO and carbamylated EPO, have organ-protective effects on the central nervous system, heart, and kidney, indicating that EPO has direct actions independent of its erythropoietic function.\textsuperscript{15,16} These findings support our conclusion that EPO has a renoprotective property independently of anemia correction.

The exact mechanism of the direct renoprotective action of EPO is not clear at this stage, but several mechanisms are considered. The first possible mechanism is the inhibitory effect of EPO on apoptosis of renal tubular cells.\textsuperscript{17} The similar mechanism has also been reported in other kidney disease models, such as acute kidney injury induced by ischemia reperfusion injury\textsuperscript{18} and lipopolysaccharide,\textsuperscript{19} puromycin aminonucleoside-induced nephrotic syndrome,\textsuperscript{20} and streptozotocin-induced diabetic nephropathy.\textsuperscript{21} The second possible mechanism is the inhibitory effect of EPO on oxidative stress injury. EPO has been reported to have direct anti-oxidative action by exploiting intracellular anti-oxidative mechanisms such as heme oxygenase-1 and glutathione peroxidase, as well as indirect anti-oxidative action by inducing iron depletion and thereby inhibiting iron-dependent oxidative injury. Such mechanisms are suggested to be involved in the renoprotective effects of ESA in acute kidney injury and CKD.\textsuperscript{22,23} The third possible mechanism is the inhibitory effect of EPO on inflammation and fibrosis. Attenuation of interstitial inflammation and fibrosis by EPO therapy has been reported in the models of chronic cyclosporine nephropathy,\textsuperscript{24} ureteral obstruction,\textsuperscript{25–27} and Thy-1 glomerulonephritis.\textsuperscript{28}

In addition, other mechanisms have been suggested to be involved in the direct renoprotective effect of EPO.\textsuperscript{29–31} Notably, darbepoetin therapy is reported to ameliorate podocyte injury and reduce proteinuria through a direct effect on podocytes.\textsuperscript{32} In the present study, no decrease in urinary protein/creatinine ratio was noted at 6 months after commencement of ESA therapy. These results make it difficult to consider that ESA made a direct effect on podocytes in our study. Instead, the efficacy could be due to some other protective action of ESA against tubulointerstitial damage in CKD, such as anti-apoptotic or anti-oxidative action.

In the CREATE, CHOIR, and TREAT studies, active ESA therapy did not show any renoprotective effect.\textsuperscript{7–9} However, the different results among these large-scale RCTs and the present study may be due to differences in clinical features and methodology. For example, the rates of cardiovascular co-morbidities, the target levels of hemoglobin, and dose of ESA were higher in these studies than ours; these factors might have unfavorable effect on the renoprotective actions of ESA.

The TREAT study\textsuperscript{9} showed almost 2-fold increased risk of stroke in the higher hemoglobin arm, whereas in the present study, the annual rate of stroke was only 0.8%. The favorable outcome in our study could be attributed to the relatively lower dosage of ESA used compared with the TREAT study. In fact, the results of a recent surveillance data published by Imai et al.\textsuperscript{33} reported no relationship between ESA therapy and stroke or cancer in Japanese patients. It is assumed that the relatively low maximum dose of ESA (24,000 units/month) approved by the Ministry of Health, Labor and Welfare in Japan, could have protected against the adverse effects of ESA, although this dose is thought to be too small to maintain hemoglobin level of 11 g/dL recommended by the guidelines for renal anemia in CKD in Japan.\textsuperscript{11}

The present study has several limitations. First, this study was conducted by a retrospective chart review and does not have a randomly assigned control group. Second, the sample size is relatively small. Third, a period of evaluation of PR was short. Forth, data on iron metabolism were not available. Nevertheless, confirmation of the hypothesis is plausible because our data are consistent with the results of the previous two recent studies reported from Japan, including one large-scale epidemiological study\textsuperscript{34} and another RCT.\textsuperscript{9} In addition, renoprotective effect of high hemoglobin levels (12.9 g/dL) using higher dose of ESA (about 6000 units/week) has been demonstrated by a RCT which has been conducted in post-renal transplant recipients with renal dysfunction and anemia.\textsuperscript{35} The dose of ESA in this RCT is similar to the maximum dose used in our study and approved in Japan until the other day, while is much lower compared to the doses used in the higher hemoglobin target groups in the CREATE, CHOIR, and TREAT studies.

In conclusion, the present study demonstrated a renoprotective effect of ESA in patients with progressive CKD. These results suggest a possibility of a direct renoprotective action of ESA independent of improvement of anemia. Further studies are needed to elucidate the mechanism of the renoprotective effect of ESA.

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