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ORIGINAL ARTICLE

Impact of very early high doses of recombinant erythropoietin on anemia and allograft function in *de novo* kidney-transplant patients

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Summary

After kidney transplantation, occurrence of anemia in the early post-transplant period (<1 month) is high and arises out of issues that are multifactorial. We performed a retrospective single-center study to assess whether delivery of high doses of erythropoietin-stimulating agents (ESA) within the first week of kidney transplantation, translates at 1 month post-transplant, in to causing less anemia and whether it has an impact on allograft function. Ninety-nine patients were not given ESA (group I), whereas 82 were (250 IU/kg/week; group II). All patients had similar pretransplant and baseline (day 0) variables. Similar numbers of group II patients were still receiving ESA by day 14 (97.5%) and day 30 (89%). Respective figures for group I were 27% and 27%. Independent factors for anemia at 1 month post-transplant included: being male subject, treatment for hypertension at pretransplant, anemia at transplant, a higher mean corpuscular volume at transplant, and an induction therapy using antithymocyte globulins. Independent predictive factors for lower creatinine clearance included being female subjects, having a donor aged >50 years, being a recipient aged >50 years, not treated for hypertension at pretransplant, and no post-transplant ESA therapy. High doses of ESA within the first month of kidney transplantation have no impact on anemia or renal function by 1 month post-transplant.

Introduction

Anemia is relatively common after kidney transplantation. Using the WHO classification for anemia, i.e. hemoglobin (Hb) levels <12 g/dl in women and <13 g/dl in men, the prevalence of post-kidney transplant anemia (PTA) after the first year ranges from 20% to 60% [1–6]. It has been recently shown that PTA cannot be solely attributed to impaired allograft function [7]. Other contributing factors, apart from allograft dysfunction, include the use of hypotensive agents such as angiotensin-converting enzyme inhibitors (ACEIs) [1], angiotensin-receptor blockers (ARBs) such as losartan [8], the type of immunosuppression (i.e. mycophenolate mofetil versus azathioprine [9]), and the use of mammalian target of rapamycin (mTOR) inhibitors [10]. The prevalence and the degree of anemia in the early post-transplant period are dependent on the pretransplantation Hb level, amount of perioperative blood loss, frequency of blood draws, iron depletion, persistence of uremia, endogenous erythropoietin (EPO)

levels, EPO responsiveness, and exposure to immunosuppressive agents [11].

Studies have shown that erythropoietin-stimulating agents (ESAs) are able to correct PTA [12–16], although only two small studies have addressed the immediate post-transplant period, i.e. within the first month [17,18]. In one study, the weekly ESA dose used was 300 IU/kg [17]. Based on this study, we chose to give early post-transplant ESA on the basis of approximately 250 IU/kg/week. Herein, we report on the results of a retrospective single-center study to assess whether the delivery of high doses of ESA immediately after kidney transplantation, i.e. within the first week, translates at 1 month post-transplant (i) in to causing less anemia in patients (anemia as defined according to the WHO criteria), and (ii) if it had an impact upon allograft function.

Patients and methods

This retrospective, single-center study evaluates two consecutive cohorts of kidney-transplant (KT) patients. All were recipients of deceased donor allograft, but there were no non heart-beating donor allografts. Participants within group I had received an allograft at our center between 1 November 2004 and 31 August 2005, and were not given ESA during the first month post-transplantation ($n = 99$), except when Hb level dropped to <8 g/dl. Patients within group II, who had received a kidney allograft between 1 September 2005 and 31 August 2006, received ESA from day 5 post-transplantation, ($n = 82$) unless Hb level was above 12 g/dl for women and 13 g/dl for men ($n = 99$, group II; see Table 1). When ESA was given, this was either as epoietin alpha or beta, at a rate of 5000 units, three times a week, i.e. approximately 250 IU/kg/week. Thereafter, the dosage was adapted to target a Hb level of ≥13 g/dl in men and 12 g/dl in women. In cases where there was poor clinical tolerance of anemia, the patient was offered a blood transfusion to increase Hb level to approximately 10 g/dl.

Most patients were receiving steroid-based and mycophenolate acid (MPA)-based immunosuppression, in addition to either calcineurin inhibitors, mTOR-Is, or belatacept. In addition, most patients received an induction therapy. This was based on antithymocyte globulins (ATGs) if the patients were sensitized against HLA antigens, or was based on anti-CD25 monoclonal antibodies if the patients were not sensitized. In cases of suspected acute rejection, a kidney biopsy was performed, and acute rejection was treated with methylprednisolone pulses (10 mg/kg/day for 3 consecutive days). In cases of

Table 1. Comparison of patients who had or did not have ESA by post-transplant day 7 as assessed by pretransplant and very early post-transplant parameters.

	ESA		
	Yes *n* = 82 (group II)	No *n* = 99 (group I)	*P*-value
Donor age (years)	45.5 ± 14.5	46.4 ± 15	NS
Donor's terminal serum creatinine (μmol/l)	92 ± 39.7	99.3 ± 48	NS
Cold-ischemia time (h)	16.9 ± 7.7	18.5 ± 9.2	NS
Recipient's age (years)	46.9 ± 13.5	49 ± 11.8	NS
Gender (M/F)	50/32	63/36	NS
CMV serostatus (D+/R–)	31.7%	26.3%	<0.0001
ESA pre-KT (yes)	47.6%	43.4%	NS
ACEIs and/or ARBs pre-KT (yes)	39%	28.2%	NS
Hb D0 (g/dl)	11.9 ± 1.3	12.2 ± 1.5	NS
MCV D0 (fl)	93.5 ± 5.7	95 ± 6.8	NS
Ferritin D0 (μg/l)	251 (10–1385)	247 (7–1705)	NS
PTH D0 (pg/ml)	187 (8–1113)	117 (10–1618)	NS
Induction therapy (yes)	78%	84.8%	NS
ATG (yes)	18.3%	31.3%	NS
DGF (yes)	30.5%	21.2%	NS
Serum creatinine (D5; μmol/l)	305 (63–1055)	284 (68–1359)	NS
Blood transfusion (number of red packed cells)	2 (0–13)	2 (0–24)	NS

ESA, erythropoietin-stimulating agent; CMV, cytomegalovirus; D, donor; R, recipient; M, male; F, female; KT, kidney transplantation; ACEI angiotensin-converting enzyme inhibitors; Y, yes; N, no; ARB, angiotensin-receptor blockers; Hb, hemoglobin; MCV, mean corpuscular volume; D0, day of transplantation; PTH, parathormone; ATG, antithymocyte globulins; DGF, delayed graft function.

steroid-resistant acute rejection, the patients were given ATG therapy.

Prophylaxis

After transplantation, in those patients at high-risk for cytomegalovirus (CMV), i.e. a seropositive donor giving to a seronegative recipient, systematic sequential prophylaxis using i.v. ganciclovir followed by oral valacyclovir or valganciclovir was given for the following 3 months. Other patients with a lower risk for CMV were closely monitored for CMV viremia by real-time polymerase chain reactions. In cases of CMV reactivation or disease, patients were treated with IV ganciclovir (10 mg/kg/day adapted to renal function) for 14–21 days. All patients received anti-*Pneumocystis jiroveci* prophylaxis during the first 6 months post-transplantation using sulfamethoxazole-trimethoprim at 80/400 mg every other day.

Data collection

Donor-related data collected were age, gender, weight, terminal serum creatinine, estimated creatinine clearance (CC; using the Cockcroft/Gault formula), CMV serostatus, and cold ischemia time. We also collected the following recipient pretransplant data: age, gender, original native kidney disease, time on dialysis, the administration or nonadministration of ESA, body mass index, the use of hypotensive medications (i.e. betablockers, diuretics, ACEIs, ARBs and vasodilating or central nervous system hypotensive agents), and CMV serostatus. We also considered the recipients' immediate post-transplant data collected on days 5, 7, 14 and 30 for factors such as Hb, mean corpuscular volume (MCV), reticulocyte count, serum creatinine and CC (according to the Cockcroft/Gault formula), the type of immunosuppressants (frequency and dosage in mg/kg/day), the use of ESAs and, if relevant, ESA weekly dosage.

Delayed graft function (DGF) was defined as the need for at least one dialysis session after day 1 post-transplant. Serum ferritin as well as parathormone levels were recorded at pretransplant and at day 30 post-transplant. CMV viremia tests were performed on a weekly basis during the first month post-transplant.

Statistical analyses

Variables are expressed either as the mean ± SD, or as a median (ranges), according to their distribution. For the univariate analysis, qualitative variables were compared by the chi-squared test or by Fisher's exact test, as appropriate. Quantitative variables were compared by Student's *t*-test or the Wilcoxon test, as appropriate. A *P*-value below 0.05 was considered statistically significant. We determined the parameters that were associated with anemia and allograft function, as assessed by serum creatinine at 1 month post-transplant. We used Student's *t*-test with two-tailed, independent samples to assess univariate analyses between the two groups, with the significance taken as $P = 0.05$. Risk factors for anemia and allograft function at 1 month post-transplant were defined using a multivariate, stepwise, logistical regression analysis that used initial inclusion criteria that had a significance of $P < 0.05$.

Results

Patients' baseline characteristics

Patients from groups I and II were comparable with respect to pretransplant and baseline (day 0) data except for CMV serostatus, with significantly more patients at risk for CMV in group II (see Table 1). At day-7 (see Table 2), the patients differed significantly for the following parameters: Hb level was lower in group II, i.e. 9.9 ± 1.32 g/dl compared to 10.54 (±1.34 g/dl) for group I ($P = 0.004$), steroid daily dose was 60 mg (20–500) in group II compared to 30 (20–80) mg in group I ($P = 0.01$), and the use of belatacept therapy was 22% in group II compared to 6% in group I ($P = 0.002$).

Post-transplant ESA therapy

Of those patients receiving ESA at post-transplant day 7 (i.e. 82), almost the same number were still receiving this by day 14 (i.e. 80:97.5%), and 79 were still receiving this

Table 2. Comparison of patients who had or did not have ESA by post-transplant day 7 with respect to day 7 post-transplant parameters.

	ESA		
	Yes *n* = 82	No *n* = 99	*P*-value
Hb at day 7 (g/dl)	9.9 ± 1.32	10.54 ± 1.34	0.004
Date of ESA initiation (days)	4.2 ± 1.9	12.5 ± 4	<0.0001
Steroids D7	95.1%	92.9%	NS
Steroids D7 (mg/days)	60 (20–500)	30 (20–80)	0.01
MPA D7	87.8%	92.9%	NS
MPA D7 ≥2g/day)	81.7%	85.8%	NS
mTOR-Is D7	9.7%	7%	NS
CsA D7	42.7%	55.5%	NS
Tac D7	28%	26.3%	NS
Belatacept D7	22%	6%	0.002

ESA, erythropoietin-stimulating agent; Y, yes; N, no; Hb, hemoglobin; D7, 7 days post-transplantation; MPA, mycophenolic acid; mTOR-Is, mTOR inhibitors; CsA, cyclosporine A; Tac, tacrolimus.

by day 30 (89%). The cumulative ESA dosage at D30 was 45 936 ± 29 547 IU (727 ± 499 IU/kg).

In group I, no patients were receiving ESA by day 7, whereas 27% required ESA by day 14 and were still receiving ESA by day 30 resulting from low Hb levels. In this group, the cumulative ESA dosage at D30 was 35 510 ± 23 260 IU (543 ± 368 IU/kg). Reticulocyte counts were significantly higher at post-transplant days 14 and 30 in group I patients as compared with those from group II, and ferritin levels at post-transplant day 30 were significantly lower in group I patients, although values remained within the normal ranges (data not shown).

The etiology of native kidney disease was similar in both group I and group II patients), i.e. glomerular disease were present in 53% and 52.4% of patients, respectively; polycystic kidney disease was found in 10.4% and 14.6% of patients respectively, and other diseases in 36.6% and 33% respectively. The percentage of patients presenting with at least one episode of acute rejection was similar in both group I (36.4%) and group II (31.7%) patients.

Predictive factors for anemia at 1 month post-transplant

Factors affecting Hb level at 1 month post-transplantation were studied. At 1 month post-transplantation, 108 patients (60.3%) were anemic, whereas 71 (39.7%) were not. Table 3 shows the pretransplant risk factors for developing anemia by 1 month post-transplant as determined by univariate analyses. These include gender (i.e. being male), lower Hb level at day 0 in males, a higher MCV at day 0, a longer cold ischemia time, the use of ATG as the induction therapy, and having pretransplant-treated hypertension.

Table 4 shows the post-transplant factors associated with anemia at 1 month post-transplantation. Significant factors associated with anemia included a high rate of anemia by day 14 in men, lower Hb by day 14 in men and women, a higher serum creatinine level by day 14, and a lower daily dose of cyclosporine by day 7 for those receiving this immunosuppressive drug. Of note, the use of ESA at either pretransplant or post-transplant (before day 30) was not predictive of anemia by day 30.

We then performed a multivariate analysis to determine the factors associated with anemia at 1 month post-transplant (Table 5). They include being male [OR: 2.4 (1.1–5); $P = 0.02$], being treated for hypertension at pretransplant [OR: 2.7 (1.2–5.8); $P = 0.01$], being anemic at transplant [OR: 2.6 (1.2–5.4); $P = 0.01$], having a higher MCV at transplant [OR: 1.1 (1.04–1.2); $P = 0.001$], and having had an induction therapy using ATG [OR: 2.6 (1.1–6.1); $P = 0.02$].

Predictive factors for kidney-allograft function at 1 month post-transplant

With regard to kidney allograft function at 1 month post-transplant, we divided the patients into those who had estimated creatinine clearance of greater or equal to 60 ml/min (according to the Cockcroft/Gault formula) ($n = 115$; 63.5%) and those who had creatinine clearance lower than

Table 3. Factors associated with anemia at 1 month post-transplantation as assessed by univariate analyses: baseline factors.

	Patients		
	with anemia	without anemia	*P*-value
Recipient age (years)	49 ± 13	47 ± 12	NS
Recipient gender (male %)	72	46	0.0009
Hb level at D0 (g/dl)			
F	11.6 ± 1.2	12.6 ± 1.5	0.006
M	11.9 ± 1.4	12.4 ± 1.6	NS
MCV D0 (fl)	96 ± 6	92 ± 7	0.005
Ferritin D0 (μg/l)	361 ± 368	437 ± 410	NS
PTH D0 (pg/ml)	211 ± 225	299 ± 345	NS
Pretransplant ESA (yes; %)	50	39	NS
Weekly ESA dosage pretransplant (IU/week)	4504 ± 2486	5340 ± 3944	NS
Donor age (years)	46 ± 15	46 ± 14	NS
Donor serum creatinine (μmol/l)	99 ± 50	92 ± 34	NS
Cold-ischemia time (h)	19 ± 8	16 ± 9	0.02
CMV prophylaxis (yes; %)	45	46	NS
Induction therapy (yes; %)	81	82	NS
ATG (yes; %)	31	16	0.02
Pretransplant hypertension (yes; %)	20	44	0.001

Hb, hemoglobin; D, day; MCV, mean corpuscular volume; PTH, parathormone; ESA, erythropoietin-stimulating agents; CMV, cytomegalovirus; ATG, antithymocyte globulins.

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Table 4. Factors associated with anemia at 1 month post-transplantation as assessed by univariate analyses: post-transplant hematologic factors.

	Patients		
	with anemia	without anemia	*P*-value
Time of the 1st ESA injection/KT (days)	7 ± 5	7 ± 7	NS
Cumulative ESA dosage at D14 (IU)	20 274 ± 18 741	22 512 ± 14 011	NS
Cumulative ESA dosage (mg/kg) at D14	310 ± 283	356 ± 239	NS
Blood transfusions at D14	2 ± 2	1.5 ± 2	NS
ESA at D7 (yes; %)	41	51	NS
ESA at D14 (yes; %)	55	55	NS
Anemia by D14 (yes; %)			
F	93	76	NS
M	100	72	<0.0001
Hb level by D14 g/dl			
F	10.6 ± 0.9	11.2 ± 1.1	0.01
M	10.4 ± 1.1	11.8 ± 1.7	<0.0001
Serum creatinine by D14 (μmol/l)	203 ± 128	155 ± 79	0.007
Delayed graft function (yes; %)	62	54	NS
Steroids D7 (yes; %)	93	97	NS
mTOR-Is D7 (yes; %)	8	10	NS
CsA D7 (yes; %)	48	52	NS
CsA (mg/kg/days) D7	4.3 ± 1.5	4.9 ± 1.8	0.04
Tac D7 (yes; %)	26	24	NS
Tac (mg/kg/days) D7	0.1 ± 0.04	0.1 ± 0.04	NS
MPA D7 (yes; %)	83	90	NS

ESA, erythropoietin-stimulating agents; KT, kidney transplantation; D, day; Hb, hemoglobin; mTOR-Is, mammalian target of rapamycin inhibitors; CsA, cyclosporine A; Tac, tacrolimus; MPA, mycophenolic acid.

Table 5. Independent factors associated with anemia at 1 month post-transplantation.

	Odd ratio	95% CI	*P*-value
Gender (male)	2.4	1.1–5	0.02
Pretransplant-treated hypertension (yes)	2.7	1.2–5.8	0.01
Anemia at D0 (yes)	2.6	1.2–5.4	0.01
High MCV at D0 (yes)	1.1	1.04–1.2	0.001
ATG therapy (yes)	2.6	1.1–6.1	0.02

CI, confidence interval; D, day; MCV, mean corpuscular volume; ATG, antithymocyte globulins.

Table 6. Independent factors associated with estimated creatinine clearance lower than 60 ml/min at 1 month post-transplantation.

	Odd ratio	95% CI	*P*-value
Gender (female)	2.48	1.06–5.83	0.03
Pretransplant-treated hypertension (no)	0.35	0.14–0.87	0.02
Donor age >50 years (yes)	2.85	1.23–6.59	0.01
Recipient age >50 years (yes)	2.4	1.05–5.47	0.03
ESA therapy post-transplant (no)	0.44	0.2–0.95	0.03

CI, confidence interval; ESA, erythropoietin-stimulating agents; CI, confidence interval; ESA, erythropoietin-stimulating agents.

60 ml/min (chronic stage 3 kidney disease) ($n = 66$; 76.5%). In univariate analysis, the significant predictive factors for having creatinine clearance lower than 60 ml/min were being female, having an older donor, being an older recipient, less likely to receive antihypertensive drugs at pretransplant, less likely to be anemic by day 14, having had more blood transfusions by day 14, more likely to be on ESA therapy by day 14, but also having had later onset of ESA therapy, having had DGF, having had more frequent serum creatinine levels >220 μmol/l by day 5, having higher serum creatinine by day 14, and more likely to have received an induction therapy.

In multivariate analysis, the independent predictive factors for having lower estimated creatinine clearance at 1 month post-transplant were being female [OR: 2.48 (1.06–5.83); $P = 0.03$], having a donor aged more than 50 years [OR: 2.85 (1.23–6.59); $P = 0.01$], being a recipient older than 50 years [OR: 2.4 (1.05–5.47); $P = 0.03$], not being treated for hypertension at pretransplant [OR: 0.35 (0.14–0.87); $P = 0.02$], and not having received post-transplant ESA therapy [OR: 0.44 (0.2–0.95); $P = 0.03$] (Table 6).

Safety

With regards to EPO side-effects, the occurrence of hypertension at 1 and 3 months post-transplant was

significantly lower in group I (58.6% and 61.6%) as compared with group II (74.4%; $P = 0.02$ and 76.8%; $P = 0.02$) respectively. The percentage of patients taking ACEIs and/or angiotensin receptor blockers as hypotensive drugs at 1 month post-transplantation was 12% in group I and 6% in group II (NS). At 3 months post-transplantation, the respective figures were 17.5% in group I and 22.7% in group II (NS). If renal arterial or renal vein thrombosis did occur, this was always before ESA was introduced. That is, before day 5 post-transplant; thus, none of these thromboses could be ascribed to the use of ESA. The incidence of deep venous thrombosis that developed within the first month post-transplantation was similar within both groups: i.e. 10.4% in group I and 8.5% in group II. Allograft loss occurred in 11 patients who did not receive ESA and in six who did receive ESA (p = ns). Eleven patients died with a functioning allograft: seven of these patients had not received ESA and four patients had received ESA. Other allograft losses were caused by chronic rejection: four patients were from the ESA(−) group and two patients were from the ESA(+) group.

Renal function and Hb levels after 1 month post-transplantation

With respect to serum creatinine levels, these were similar in both groups at 3 months post-transplantation [124 (63–248) μmol/l in group I and 125 (60–208) μmol/l in group II], at 6 months post-transplantation [126 (66–251) μmol/l in group I and 129 (69–225) μmol/l in group II], and at 12 months post-transplantation [126 (63–318) μmol/l in group I and 123 (70–296) μmol/l in group II]. Whereas at 3 months post-transplantation, Hb levels were similar in group I (12.9 (8.5–18.2) g/dl) and in group II (12.8 (9.1–16.9) g/dl), Hb levels were statistically lower in group II at 6 [12.6 (7–16) g/dl; $P = 0.02$] at 12 [12.9 (8.6–18) g/dl; $P = 0.003$] months post-transplantation compared to group I patients [13.4 (9.5–16.6) and 13.8 (8.6–16.8) g/dl respectively].

Discussion

In this retrospective single-center study we found that, at 1 month post-kidney transplantation, 60% of KT patients had PTA that was not influenced by the use of high doses of ESA in the very early post-transplant period. Moreover, we found that the use of ESA therapy within the first month post-transplantation had no beneficial impact upon kidney allograft function at 1 month post-transplantation.

From various literature studies, the prevalence of PTA is reported to vary from 20% to 60% [19]. This wide range of PTA rates is caused, first, by the use of different definitions for PTA and, second, because PTA is looked for between the first months of post-transplantation to years after post-transplantation. However, when PTA is looked for within the first month of post-transplantation, the prevalence is 70% [5], which is very close to our value (60%).

After kidney transplantation, the time-course of erythropoiesis has been studied and it has been shown that, after a transient early peak of EPO (24 h after transplantation) that is not associated with a measurable increase in Hb level, within a few days a smaller but more sustained EPO peak is detectable and is associated with the subsequent onset of erythropoiesis and recovery from renal anemia [20]. In addition, cases of onset of acute graft rejection within the first month post-transplantation abrogate the hematopoietic response until the rejection is successfully reversed [21]. Recovery from renal anemia can also be hampered by various factors, such as impaired allograft function, or the use of an immunosuppressive drug that can alter erythropoiesis, e.g. mTOR-Is [10] or antimetabolites [9]. Nonetheless, in maintenance kidney-transplant patients presenting with PTA, the use of ESA has been shown to be efficient. Studies have shown that ESA is able to correct PTA [12–16], despite the fact that, to date, no prospective trial has compared ESA versus 'no therapy', with the endpoints being correction of anemia or anemia-related effects such as left ventricular function/remodeling. Conversely, with respect to treating very early PTA, i.e. occurring within the first month post-transplant, only two trials have been conducted so far [17,18].

In one of these studies [17], the patients were randomized to receive ($n = 22$) or not receive ($n = 18$) ESA at 100 IU/kg three times a week, if Hb level was less than 12.5 g/dl. The time to recover Hb levels greater than 12.5 g/dl was 66.5 ± 14.5 in the non-ESA group vs. 52.6 ± 23.7 days in the ESA group ($P = 0.05$). After 3 months, there were no Hb-level differences between the two groups. In the ESA group, 14 out of 22 patients reached the target Hb level of greater than 12.5 g/dl as compared with 12 out of 18 patients in the non-ESA group (NS). Also, renal function did not differ between the two groups. The authors concluded that the use of ESA in the immediate post-transplant period had no relevant clinical impact on the correction of anemia after transplantation [17]. In the other study [18], the patients were randomized to either receive lower ESA doses (150 IU/kg/week; $n = 14$) or no ESA ($n = 15$). ESA was started when hematocrit was lower than 30%. In the treated group, hematocrit significantly increased as compared with the control group between transplantation and 4 weeks post-transplantation. The maximum ESA dose after transplantation was more than two times higher

than that given before transplantation, i.e. 197.1 ± 45.1 vs. 85 ± 76 IU/kg/week; $P < 0.05$ [18]. These authors concluded that ESA could safely and effectively correct anemia during the first weeks after kidney transplantation despite relative EPO resistance.

In our study, the weekly doses of ESA that we used were greater because we started on a weekly basis of 250 IU/kg, which was increased up to a cumulative ESA dose of 727 ± 499 IU/kg at day 30. Despite this high dose, the use of ESA was not associated with an improved Hb level by 1 month post-transplant. This highlights the fact that *de novo* KT patients exhibit ESA resistance during the first month post-transplant. The factors responsible for this resistance are probably numerous. For example, we could not assess the role of mycophenolic acid in this ESA resistance because all of our patients were receiving a regimen that contained this drug; however, mycophenolic acid has been associated with rare cases of pure red-cell aplasia [22].

Moreover, very few of our patients were receiving mTOR-Is-based immunosuppression; we know that this class of immunosuppressants is more likely to induce PTA than a regimen based on mycophenolic acid [10]. In addition, in our study we found that an induction therapy with ATGs was an independent factor for developing anemia by 1 month post-transplant: it increased the risk by 2.6-fold [OR: 2.6 (1.1–6.1); $P = 0.02$]. Hence, it has recently been reported that, depending on the dose of ATG, the prevalence of anemia can vary considerably from 29.4%, when ATG is given at 0.5 mg/kg/day, to 62.5%, when ATG is given at 2 mg/kg/day [23]. Our patients received ATG at 1.12 mg/kg every other day.

Having anemia at pretransplant was also an independent risk factor for having anemia at 1 month post-transplant, giving an increased risk of 260%. This is a fully acknowledged risk factor [11]. Moreover, the higher the MSV at pretransplant, the higher the likelihood of having anemia at 1 month post-transplant, i.e. it gives an independent increase risk of 10%. As we did not assess pretransplant vitamin B9 or vitamin B12 levels we cannot ascribe this risk to a deficit of these vitamins (which are needed for erythropoiesis). Finally, we found that male gender was an independent predictive factor for having anemia at 1 month post-transplant, giving an increased risk of 240%. This is at odds with previous studies that identified female gender as an independent risk factor for PTA. However, in those studies, the patients were monitored when they were at least 3 months post-transplant whereas our patients were monitored within the first month post-transplant [24,25].

The EPO receptor is present in the glomerulus, mesangial, and tubular epithelial cells in the kidney. The experimental use of epoietin in animal models of acute renal failure has shown that it attenuates the dysfunction and histological changes associated with ischemia-reperfusion injury, with a reduction in apoptotic cell death [26]. *In vitro* studies have shown that epoietin has direct effects on proliferation and cell death in proximal tubular epithelial cells [26]. Epoietin has also shown benefits in animal models of systemic shock and cisplatin-induced nephrotoxicity [27], and in renal injury induced by aortic ischemia-reperfusion in a rat model [28]. Darbepoetin-alfa has exhibited comparable renoprotection to that afforded by epoietin in an ischemic renal injury model [29]. However, in humans and particularly immediately after kidney transplantation, which is a model of ischemia/reperfusion, so far there has been no evidence to support the fact that high doses of ESAs have renoprotective effects.

In our study, we divided the patients at 1 month post-transplant on the basis of their estimated glomerular filtration rate (GFR), based on the Cockcroft–Gault formula. We defined those as having worse renal function when estimated GFR was lower than 60 ml/min, i.e. stage 3 chronic kidney disease. However, the use of ESA within the first month post-transplant increased the risk for having lower estimated GFR at 1 month post-transplant by 54%. Thus, these results should be treated with caution as the study was neither prospective nor randomized. The other independent predictive factors associated with poorer GFR at 1 month post-transplantation were being female [OR: 2.48 (1.06–5.83); $P = 0.03$], having a donor aged more than 50 years [OR: 2.85 (1.23–6.59); $P = 0.01$], being a recipient older than 50 years [OR: 2.4 (1.05–5.47); $P = 0.03$], which are known identified factors, and not being treated for hypertension at pretransplant [OR: 0.35 (0.14–0.87); $P = 0.02$].

We conclude from this retrospective study that high doses of ESA given within the first month of post kidney transplantation has no impact upon anemia at this time, and might also affect kidney-allograft function.

Authorship

NK: designed the study, did follow-up of patients, performed the statistical analysis, and participated to writing the paper. AH: collected the data. OC, LE, IC, LL, JG: did the follow-up of patients. LR: designed the study, did follow-up of patients, and wrote the paper.

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