American Journal of Transplantation 2003; 3: 835–845
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ISSN 1600-6135

Prevalence and Management of Anemia in Renal Transplant Recipients: A European Survey

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The TRansplant European Survey on Anemia Management (TRESAM) documented the prevalence and management of anemia in kidney transplant recipients. Data from 72 transplant centers in 16 countries were screened, involving 4263 patients who had received transplants 6 months, 1, 3 or 5 years earlier. The mean age of transplant recipients was 45.5 years at transplantation. The most common etiology was chronic glomerulonephritis. The most common comorbidities were coronary artery disease, hepatitis B/C, and type 2 diabetes. The mean hemoglobin levels before transplantation were significantly higher in the more recently transplanted recipients. At enrollment, 38.6% of patients were found to be anemic. Of the 8.5% of patients who were considered severely anemic, only 17.8% were treated with epoetin. There was a strong association between hemoglobin and graft function; of the 904 patients with serum creatinine >2 mg/dL, 60.1% were anemic, vs. 29.0% of those with serum creatinine ≤2 mg/dL ($p < 0.01$). Therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, mycophenolate mofetil (MMF) or azathioprine was also associated with a higher likelihood of anemia. The prevalence of anemia in the transplant recipients was remarkably high and appeared to be associated with impaired renal function and with ACE inhibitors and angiotensin II receptor antagonist use. Further studies should be carried out to interpret whether appropriate management of anemia after kidney transplantation may improve long-term outcome.

Key words: Anemia, epoetin, hemoglobin, immunosuppressive treatment, kidney transplantation, chronic kidney disease

Received 24 September 2002, revised 14 January 2003 and accepted for publication 12 February 2003

Introduction

Renal transplantation is considered the treatment modality of choice for patients with chronic renal failure. In recent years, advances in transplantation management, especially related to immunosuppressive therapy, have increased the 1-year patient survival rate to greater than 95% and the 1-year graft survival rate to greater than 90% (1). Patients with a well-functioning renal graft will also enjoy a significantly better quality of life compared with patients on long-term hemodialysis or peritoneal dialysis (2).

Quality of life of renal transplant recipients can be affected by many factors. Apart from the comorbidities that are present before transplantation, patients are likely to suffer from both the short-term and long-term side effects of chronic immunosuppressive therapy. In addition, in the majority of transplant recipients, the renal graft does not function optimally, with the result that the excretory and endocrine functions are not restored completely. Although hemoglobin (Hb) levels will generally increase after transplantation, anemia can persist in patients with a graft that functions suboptimally (3).

Anemia in kidney transplant recipients may also negatively affect long-term outcome. Anemia in patients who undergo dialysis has been linked to the development of left ventricular hypertrophy, and is believed to be a major contributor to cardiovascular risk (4,5). Anemia may also be a cardiovascular risk factor in post-transplant recipients, which is particularly worrying because cardiovascular events are known to be the main cause of death in transplant recipients (6).

At present, there is little insight into the prevalence and management of anemia in the renal transplant population. The main goal of the Transplant European Survey on

Anemia Management (TRESAM) was to create a large European database to document the prevalence and risk factors of anemia, as well as current treatment practices in transplant centers across Europe.

Patients and Methods

Survey design and patient population

The survey used a descriptive correlational design. Inclusion criteria for the participating transplant centers (72 centers in 16 European countries) included a minimum of 5 years' experience performing renal transplants and a minimum activity of 40 kidney transplants per year.

During the survey enrollment period from 15 November 2000 through 31 May 2001, participating centers screened all kidney transplant recipients who received a transplant from 6 months up to 5 years ago. Exclusion criteria were multiple organ transplantation, pregnancy at the time of enrollment, and age less than 10 years at the time of enrollment. Patients were included into one of four cohorts, depending on when their transplant had been performed: 6 months (± 1 month), 1 year (± 1 month), 3 years (± 3 months) or 5 years (± 3 months) previous. Centers were instructed, once they had started to include the first patient from each cohort into the survey, to include all consecutive patients who received transplants in that corresponding period and who met the inclusion criteria. Centers were also asked to include in each of the four cohorts an equal number of patients. For patients no longer followed in the transplant center, the data were obtained through the physician in charge of the patients (mostly the referring nephrologist).

Measurements

Demographic and historical data collected at enrollment included age, gender, etiology of chronic renal failure, and comorbidities. Transplant-related data included: number of previous transplants, age of donor of current transplant, donor type (living or cadaveric), number of treated acute rejection episodes since the most recent transplant, and the most recent Hb measurement before transplantation. Current clinical and laboratory data for the patients in the four cohorts included body weight, blood pressure, current smoking status, performance status (WHO score with 0 being the most optimal and 4 being the least optimal performance), Hb, serum ferritin, serum albumin, percent transferrin saturation, parathyroid hormone (PTH), serum creatinine, 24-h proteinuria, measured (24-h urine) creatinine clearance, calculated creatinine clearance, homocysteine, triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol. Data on epoetin levels were not collected. The following recent clinical events (occurring within 3 months of the enrollment date) were included: infection treated with antibiotics, cerebrovascular accident (CVA), chronic blood loss, severe acute blood loss, cardiac failure, myocardial infarction, peripheral vascular disease (PVD), neoplasia, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG).

Patients' use of maintenance immunosuppressives [steroids, cyclosporine, tacrolimus, mycophenolate mofetil (MMF), azathioprine or sirolimus], antihypertensives [angiotensin-converting enzyme (ACE) inhibitors, vasodilators, beta-blockers, angiotensin II receptor antagonists, calcium channel blockers, alpha-1 antagonists, diuretics and clonidine] or other medications (antibiotics, aspirin, oral anticoagulants, insulin, oral antihyperglycemics, H_2 blockers, statins, antiepileptics, and theophylline) was assessed. Only use of the above-mentioned drugs (yes or no) was assessed, not the daily dose. Anemia management therapies in the month before enrollment [administration of recombinant human erythropoietin (rHuEPO/epoetin), iron supplementation and blood transfusions] were also assessed.

Following the Clinical Practice Guidelines for Outpatient Surveillance of Renal Transplant Recipients, anemia was defined as Hb levels of $\leq$13 g/dL for males and $\leq$12 g/dL for females. (7). Anemic patients were further subdivided into three subcategories based on the severity of the anemia:

I. Mild: males: Hb $>$ 12 g/dL and Hb $\leq$ 13 g/dL, females: Hb $>$ 11 g/dL and Hb $\leq$ 12 g/dL

II. Moderate: males: Hb $>$ 11 g/dL and Hb $=$ 12 g/dL, females: Hb $>$ 10 g/dL and Hb $=$ 11 g/dL

III. Severe: males: Hb $\leq$ 11 g/dL, females: Hb $\leq$ 10 g/dL

Creatinine clearance was calculated using the Cockcroft-Gault formula (8). Measured creatinine clearance was determined from a 24-h urine collection.

The impact of risk factors other than kidney function on anemia was assessed in a subgroup that excluded those patients in whom anemia was already associated with poor kidney function. These risk analyses were performed on the data from the 3359 patients who had serum creatinine levels up to 2 mg/dL.

Statistical analyses

Data assessment and descriptive statistics were performed on all study variables. The Chi-square test was used to test the difference in proportions in two or more groups. Relevant statistical tests were used to evaluate differences between cohorts and other stratifications. After exploring distribution and statistical assumptions, parametric and non-parametric tests were used where appropriate.

Differences between group means for interval level variables that were normally distributed were tested using either the *t*-test (two samples) or analysis of variance (ANOVA; more than two samples). As ANOVA shows an overall difference, further post-hoc ANOVA Tukey tests were performed to determine between which groups differences existed. For variables with non-normal distributions, the Mann–Whitney *U*-test (two samples) or the Kruskal–Wallis test (more than two samples) were used. Again, the (ranked) post-hoc Tukey test was performed to determine specifically between which groups differences existed.

To determine whether a relationship existed between two interval/ratio level variables, a Pearson's correlation was utilized if the distribution was normal. Associations between non-normally distributed variables were tested using Kendall's tau.

Finally, an associative logistic regression was used to explore the relationship between anemia and the following variables: age of recipient $>$ 60 years, age of donor $>$ 60 years (yes/no), serum creatinine $>$ 2 mg/dL (yes/no), use of ACE inhibitors or angiotensin II receptor antagonists (yes/no), use of azathioprine and/or MMF (yes/no), and polycystic kidney disease (yes/no).

For all statistical tests, a probability value of alpha 0.05 or less was considered significant. All analyses were conducted on the total sample and on the four transplant cohorts (6 months, 1, 3 and 5 years). Reported percentages are computed based upon patients with valid data on a test-by-test basis. All statistical analyses were performed using SPSS 9.0® (SPSS Inc., Chicago, IL, USA).

Results

Demographics and baseline characteristics

The total sample consisted of 4263 patients from the following countries: Austria (2.3%), Belgium (8.6%), Bulgaria (1.9%), Czech Republic (3.0%), Finland (1.7%), Germany (19.8%), Hungary (6.8%), Italy (5.3%), the Netherlands (1.6%), Norway (1.5%), Poland (3.3%), Portugal (3.3%), Spain (26.3%), Sweden (2.5%), Switzerland (3.0%), and the UK (9.1%). The patient characteristics in Table 1 indicate that the survey was performed in a representative European transplant population.

The 4263 patients in the total sample were more or less evenly distributed over the four cohorts: 1003, 960, 1254 and 1046 patients, respectively, were enrolled in the transplant cohorts of 6 months, 1, 3 and 5 years after transplantation. There were 2641 male patients (62.0%) and 1622 female patients (38.0%), and these proportions were similar in the four cohorts. Patients who received a transplant more recently had a higher mean age at transplantation than patients transplanted earlier (Table 1).

A total of 3823 patients (89.7%) received a kidney from a cadaver donor and 440 patients (10.3%) received a kidney from a living donor, and these proportions were similar in the different cohorts. The mean age of all donors was 43.6 ± 15.8 years; the mean age of living donors (49.0 ± 11.5 years) being significantly higher ($p < 0.01$) than the mean age of cadaveric donors (42.9 ± 16.1 years) (Table 1). In total, 1598 donors were aged > 50 years [1394 (87.2%) cadaveric donors, 204 (12.8%) living], and the proportions cadaveric and living donors > 50 years were similar in the different cohorts. The median age was 50 and 45 years, respectively, for the living and cadaveric donors.

Interestingly, the mean age of the donors significantly increased in the more recent years (40.6 ± 15.9 in the 5-year cohort vs. 43.3 ± 16.0 and 45.0 ± 16.8 in the 6-month and 1-year cohorts, respectively). Also, a greater proportion of more recent transplants was a second transplant (13.1% in the 6-month cohort vs. 10.1% in the 5-year cohort). The incidence of treated acute rejections was lower in the more recent years, when new immunosuppressive drugs became available. Mean body weight was lower in the 6-month cohort than in the other cohorts (Table 1).

The most prevalent underlying kidney disease was chronic glomerulonephritis (ranging from 29.8 to 37.0% across the four cohorts). In descending order, the next most prevalent underlying diseases were polycystic kidney disease (10.9–14.0% across the cohorts), tubular interstitial nephropathy (7.2–11.0%), diabetic nephropathy (6.5–7.5%), renal vascular disease (3.7–5.5%), systemic diseases (2.8–4.4%), and other hereditary diseases (2.2–3.9%). Other underlying kidney diseases accounted for 9.8–14.1% across the four cohorts, and disease of undefined etiology was present in 12.3–14.6% of the patients.

Across the four cohorts, the most frequently occurring comorbidities were coronary artery disease (13.0–16.1%), hepatitis B carrier or presence of anti HCV antibodies (9.3–10.8%), and type 2 diabetes (8.7–10.1%). The prevalences of post-transplant polycythemia in the 6-month, 1-year, 3-year and 5-year cohorts were 3.5%, 4.7%, 8.7% and 8.8%, respectively, (6.6% overall). In descending order, other comorbidities were chronic cardiac arrhythmia (4.6–6.5%), type 1 diabetes (4.4–5.7%), chronic bacterial infection (3; 1–5.0%), malignant neoplasia (excluding nonmelanoma skin cancer) (3.2–4.5%), chronic obstructive pulmonary disease (2.8–3.8%), and other chronic inflammatory diseases (2.3–3.5%).

During the 3 months before enrollment, infection (treated with antibiotics) was the most common clinical event in all four cohorts (13.1–25.0%), followed in frequency by CABG (2.7–7.9%), PVD (2.3–3.7%), cardiac failure (1.3–1.7%) and chronic blood loss (1.0–1.2%). Other clinical events were neoplasia (0.6–1.0%), severe acute blood loss (0.6–1.3%), CVA (0.4–0.8%), PTCA (0.3–0.7%) and myocardial infarction (0.1–0.5%). A history of active smoking was reported in 25.5–31.6% of the patients across the four cohorts.

Prevalence of anemia

Hemoglobin concentrations at the time of transplantation were significantly higher in patients who received a transplant more recently: in patients who received kidney transplants 6 months, 1, 3 and 5 years earlier, the mean Hb levels before transplantation were 11.9 ± 1.7 g/dL, 11.7 ± 1.8 g/dL, 11.2 ± 1.8 g/dL and 10.8 ± 1.8 g/dL, respectively ($p < 0.01$).

At the time of enrollment, the mean Hb levels were 13.2 ± 1.9 g/dL for the total sample (Table 2). Figure 1 illustrates the distribution of Hb levels for each cohort at the time of the survey. Overall, Hb levels ranged from 4.5 to 20.1 g/dL. A small but statistically significant difference was found between the mean Hb levels of patients who received transplants 6 months ago (13.0 ± 1.8 g/dL) compared with those who received transplants 1 year ago (13.3 ± 1.0 g/dL) ($p < 0.01$) and 3 years ago (13.2 ± 1.9 g/dL) ($p = 0.05$). In the total sample, 1645 patients (38.6%) were found to be anemic. Of these patients, 786 (18.4% of total population) had mild anemia, 495 (11.6% of total) had moderate anemia, and 364 (8.5% of total) had severe anemia.

Risk factors for anemia

Although the female transplant recipients had lower mean Hb levels (12.6 ± 1.7 g/dL) than the male patients (13.5 ± 1.9 g/dL) ($p < 0.01$), prevalence of anemia did not differ by gender (in the whole group or by cohort) (Figure 2).

Table 1: Characteristics of the transplant cohorts

		Total sample n = 4263	6 months n = 1003 (23.5%)	1 year n = 960 (22.5%)	3 years n = 1254 (29.4%)	5 years n = 1046 (24.5%)	Significance testing*
Recipient gender	Male	2641 (62.0%)	622 (62.0%)	583 (60.7%)	804 (64.1%)	632 (60.4%)	p = NS
	Female	1622 (38.0%)	381 (38.0%)	377 (39.3%)	450 (35.9%)	414 (39.6%)	
Recipient age (years)	At enrollment[a]	48.0 ± 13.0	46.6 ± 13.1	48.4 ± 13.0	48.1 ± 12.7	48.7 ± 13.3	p < 0.01
	At transplantation[a]	45.5 ± 13.1	46.1 ± 13.1	47.3 ± 13.0	45.1 ± 12.7	43.6 ± 13.2	p = 0.01
Donor type	Cadaveric	3823 (89.7%)	885 (88.2%)	858 (89.4%)	1122 (89.5%)	958 (91.6%)	p = NS
	Living	440 (10.3%)	118 (11.8%)	102 (10.6%)	132 (10.5%)	88 (8.4%)	
Transplant number	First	3705 (86.9%)	849 (84.6%)	853 (88.9%)	1092 (87.1%)	911 (87.1%)	p < 0.05
	Second	471 (11.0%)	131 (13.1%)	93 (9.7%)	141 (11.2%)	106 (10.1%)	
	Third	87 (2.0%)	23 (2.3%)	14 (1.5%)	21 (1.7%)	29 (2.8%)	
Number of treated acute rejections [b]		0.5 ± 1.4 (0)	0.4 ± 0.8 (0)	0.4 ± 1.7 (0)	0.5 ± 1.7 (0)	0.6 ± 1.0 (0)	p < 0.01
Donor age (years)	Cadaveric[a]	42.9 ± 16.1	43.3 ± 16.0	45.0 ± 16.8	43.0 ± 15.7	40.6 ± 15.9	p = 0.01
	Living[a]	49.0 ± 11.5	50.0 ± 10.9	48.5 ± 12.7	49.9 ± 10.3	46.9 ± 12.1	p = NS
Blood pressure at time of enrollment	Systolic (mmHg)[a]	137.4 ± 18.1	137.3 ± 18.6	137.1 ± 18.2	137.5 ± 17.6	137.7 ± 18.0	p = NS
	Diastolic (mmHg)[a]	81.2 ± 10.2	80.8 ± 10.2	80.9 ± 10.2	81.6 ± 10.0	81.1 ± 10.3	
Body weight at time of enrollment (kg)[a]		73.1 ± 14.7	71.7 ± 14.5	73.9 ± 14.4	73.6 ± 14.8	73.1 ± 14.8	p < 0.01
WHO performance score[b]		0.5 ± 0.8 (0)	0.5 ± 0.8 (0)	0.5 ± 0.8 (0)	0.6 ± 0.8 (0)	0.5 ± 0.8 (0)	p = NS

*Chi-square, ANOVA or Kruskal–Wallis was used where appropriate.
[a]Mean ± SD; [b]Mean ± SD (median).

Table 2: Mean hemoglobin and creatinine concentrations at the time of enrollment for each transplant cohort

	Total sample n = 4263	6 months n = 1003	1 years n = 960	3 years n = 1254	5 years n = 1046	Significance testing*
Hemoglobin (g/dL)[a]	13.2 ± 1.9	13.0 ± 1.8	13.3 ± 1.9	13.2 ± 1.9	13.2 ± 1.9	$p < 0.01$
Serum creatinine (mg/dL)[b] (median)	1.7 ± 1.0 (1.5)	1.6 ± 0.6 (1.4)	1.6 ± 0.8 (1.5)	1.8 ± 1.0 (1.6)	1.8 ± 1.2 (1.5)	$p < 0.01$
Measured creatinine clearance (mL/min)[a]	60.9 ± 27.3	62.4 ± 28.2	64.3 ± 28.0	59.5 ± 26.3	57.7 ± 26.4	$p < 0.01$

*ANOVA or Kruskal–Wallis was used where appropriate.
[a]Mean ± SD.
[b]Mean ± SD (median).

A relationship between age of the recipient and Hb levels was not found. Hb levels were higher in patients who received a first kidney transplant (13.2 ± 1.9 g/dL) than in those who received a second (12.8 ± 1.9 g/dL) or third transplant (12.7 ± 2.1 g/dL) ($p < 0.01$). Patients who had experienced more episodes of treated acute rejections had lower mean Hb levels: patients without rejection episodes had mean Hb levels of 13.3 ± 1.9 g/dL, whereas those who had experienced one rejection had mean Hb levels of 13.1 ± 1.9 g/dL, and patients with two, three, four or more rejections had mean Hb levels of 12.5 ± 1.9 g/dL, 12.3 ± 1.8 g/dL, 11.6 ± 2.2 g/dL and 12.8 ± 2.0 g/dL, respectively ($p < 0.01$).

The mean (± SD) serum creatinine concentration for the entire sample was 1.7 ± 1.0 mg/dL (median 1.5 mg/dL) (Table 2). Patients who received transplants 3 years ago had significantly higher serum creatinine concentrations than patients in the other cohorts ($p < 0.01$) (Table 2). Measured creatinine clearance was significantly higher in patients in the 1-year cohort than in patients in the 3-year ($p = 0.05$) and 5-year ($p < 0.01$) cohorts (Table 2). No correlation existed between

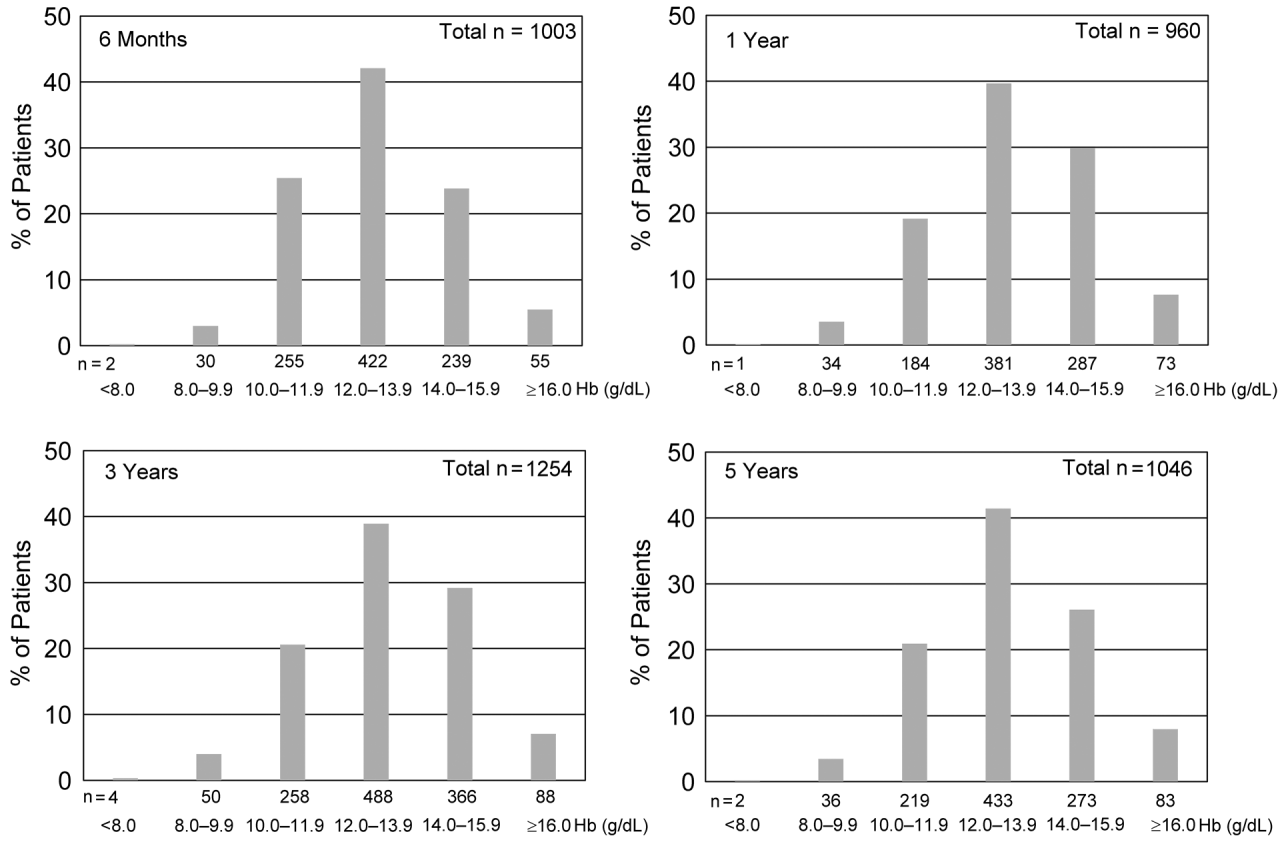

Figure 1: Hemoglobin levels in each of the four cohorts. Distribution of mean Hb levels (in g/dL) in the patient cohorts who received kidney transplants 6 months, 1, 3, or 5 years earlier.

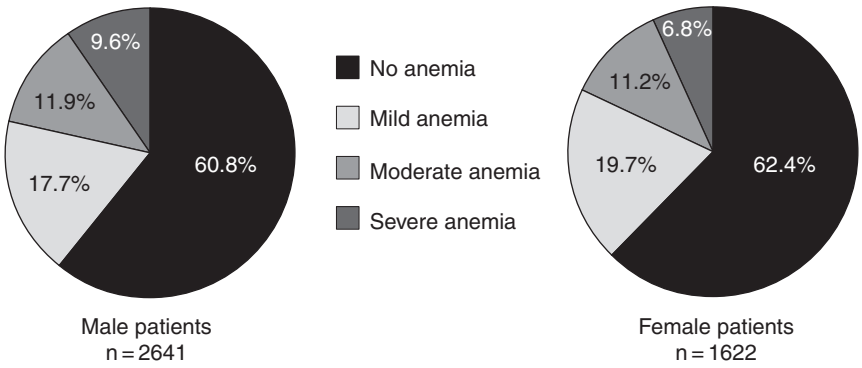

Figure 2: Anemia by gender. Prevalence of mild, moderate and severe anemia in the total patient sample (n = 4263) divided by gender.

the age of the recipient and serum creatinine. Creatinine clearance and Hb concentrations decreased significantly with increasing donor age ($p < 0.01$). While higher Hb concentrations were correlated with improved creatinine clearance rates the strength of this relationship weakened with increasing donor age.

Patients not treated with epoetin had lower Hb levels if serum creatinine was high ($p < 0.01$) or creatinine clearance was low ($p < 0.01$; Figure 3). Of the 904 patients with serum creatinine levels > 2 mg/dL, a significantly greater proportion were anemic (62.8%, sum of 21.0% with mild, 21.5% with moderate, and 20.4% with severe anemia) compared with patients with serum creatinine levels ≤ 2 mg/dL (32.1%) ($p < 0.01$).

Steroids and cyclosporine were the most commonly used immunosuppressive agents (used by 84.5% and 66.6% of patients, respectively) (Table 3). The differences in the four cohorts reflect the changes in immunosuppressive therapies available in Europe. The combination of cyclosporine, steroids and MMF was the most often used combination therapy (30.7%) (Table 3). Mean Hb levels in patients treated with combination therapies ranged from 12.6 ± 1.6 g/dL (steroids and MMF) to 13.5 ± 1.9 g/dL (tacrolimus and steroids) (Table 4).

Azathioprine and MMF are immunosuppressives that may induce anemia (9). A significant difference in Hb levels was found in patients treated with MMF, or combinations including MMF, compared with patients not treated with MMF (13.1 ± 1.9 g/dL vs. 13.4 ± 2.0 g/dL, respectively, $p < 0.01$) (Table 5). No such difference was found for azathioprine in the total patient sample (Table 5). In the subgroup of patients with serum creatinine levels ≤ 2 mg/dL, however, a significant difference in Hb levels (0.2 g/dL) was found between patients treated with or without azathioprine ($p < 0.05$).

Of those cases with complete medication data (n = 3631), 1408 patients (38.8%) received a combination of calcium-channel blockers, steroids, and either tacrolimus or cyclosporine. The proportion of patients treated with this combination of medications was significantly higher ($p < 0.01$) in the 6-month cohort (43.8%) compared with the 1-year (36.7%), 3-year (39.9%) or 5-year (34.3%) cohorts. Patients on this regimen had higher Hb levels (13.5 ± 1.9 g/dL) than patients not receiving this treatment (13.0 ± 1.9 g/dL) ($p < 0.01$).

Of the antihypertensive treatments, beta-blockers were prescribed most frequently (47.4% overall), followed by calcium-channel blockers (47.1%) and diuretics (29.1%). Other antihypertensives included ACE inhibitors (25.9%), alpha-1 antagonists (18.5%), angiotensin II receptor antagonists (10.3%), vasodilators (7.8%) and clonidine (5.3%). For the total sample, there were no significant differences in Hb levels between patients treated with ACE inhibitors (13.1 ± 1.9 g/dL) and those not given ACE inhibitors (13.2 ± 1.9 g/dL). Anemic patients treated with ACE inhibitors, however, had only slightly but statistically significantly higher Hb levels (11.7 ± 1.4 g/dL) than anemic patients not treated with ACE inhibitors (11.4 ± 1.1 g/dL) ($p < 0.01$). Patients treated with angiotensin II receptor antagonists had significantly lower Hb levels (12.9 ± 2.0 g/dL) than patients not treated with angiotensin II receptor antagonists (13.2 ± 1.9 g/dL) ($p < 0.01$).

Many patients also received H_2 blockers (42.2%), statins (34.1%), aspirin (22.7%), antibiotics (16.4%), insulin (10.3%), oral anticoagulants (6.6%), oral antihyperglycemics (3.6%), antiepileptics (1.5%) or theophylline (0.8%).

Recent infections had an impact on the occurrence of anemia; the mean Hb of patients who had experienced recent infections was 12.5 ± 2.3 g/dL vs. 13.0 ± 2.0 g/dL in patients who had not had recent infections ($p < 0.001$). Hepatitis B or C, on the other hand, did not have an impact on anemia (mean Hb of patients with hepatitis B or C was 13.1 ± 2.2 g/dL vs. 13.0 ± 2.1 g/dL in patients without hepatitis B or C, $p = 0.134$). Hb concentrations were also significantly correlated with the occurrence of clinical events (including infections, CVA, chronic blood loss, cardiac failure, myocardial infarction, PVD, new-onset neoplasia, surgery including PTCA). The mean Hb of patients who experienced at least one clinical event was significantly lower than that of

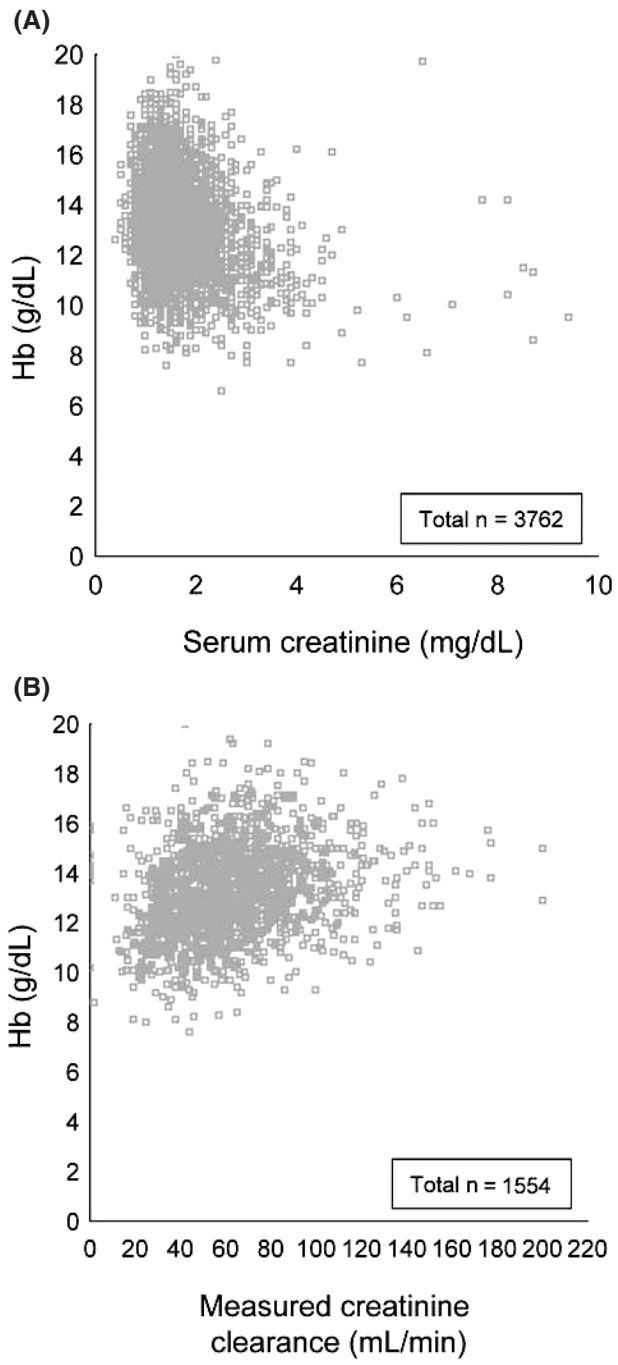

Figure 3: Hemoglobin level and kidney function. Relationship between hemoglobin levels and kidney function expressed as serum creatinine concentration (A) and measured creatinine clearance (B) in patients not treated with epoetin.

patients who had not experience any clinical event (12.6 ± 2.2 g/dL vs. 13.1 ± 1.0 g/dL, $p < 0.01$).

Associative logistic regression was used to determine the relationship between anemia as a nominal variable and the following variables: age of donor > 60 years (yes/no), serum creatinine > 2 mg/dL (yes/no), presence of a recent infection, use of ACE inhibitors or angiotensin II receptor antagonists (yes/no), use of azathioprine and/or MMF (yes/no) and polycystic kidney disease (yes/no). Collectively, these variables accounted for 11.4% of the variance in anemia. The goodness of fit test indicated adequate fit of the model to the data and the overall correct classification was 68.6%. Results indicate that the odds of being anemic were 3.48 times greater in patients with serum creatinine levels > 2 mg/dL than in those patients whose serum creatinine was ≤ 2 mg/dL (Table 6). Use of ACE inhibitors or angiotensin II receptor antagonists was also associated with a higher odds ratio for being anemic (odds ratio = 1.55) as was donor age > 60 years (odds ratio = 1.41). When comparing nonanemic with severely anemic patients, the model achieved an 88.10% classification accuracy rate. The odds ratios obtained for this model are given in Table 7. Serum creatinine (> 2 mg/dL), use of ACE inhibitors or angiotensin II receptor antagonists, and a recent infection significantly increased the risk of severe anemia, while polycystic kidney disease as original diagnosis was protective ($p < 0.05$).

Anemia management

Of the 3969 patients for whom epoetin use (yes/no) was documented, 207 patients (5.2%) received epoetin for treatment of anemia. Of the 2430 nonanemic patients for whom epoetin use was documented, 47 (1.9%) received epoetin. Of the 731 patients with mild anemia, 44 (6.0%) were treated with epoetin, of the 465 patients with moderate anemia 55 (11.8%) were treated with epoetin, and of the 343 patients with severe anemia 61 (17.8%) were treated with epoetin. The mean Hb level in patients receiving epoetin was significantly lower than in patients not receiving epoetin (11.1 ± 2.0 g/dL vs. 13.1 ± 2.1 g/dL, $p < 0.01$). Rates of epoetin administration in the cohorts of 6 months, 1 year, 3 years and 5 years post-transplantation were similar (4.0%, 5.5%, 5.4% and 5.8%, respectively; p = NS). The median epoetin dose that was administered in the total sample was 4000.0 IU/week (mean ± SD: 5831.7 ± 4217.4 IU/week).

Performance status and anemia

Overall, the performance status of kidney transplant recipients, as measured by the WHO score, was good with a median score of 0 (mean ± SD 0.5 ± 0.8) (with WHO score 0 being the most optimal and 4 being the least optimal performance). The performance status of patients with severe anemia (mean ± SD 0.9 ± 1.0, median 1) was significantly different from those of patients without anemia or with mild or moderate anemia (all median 0, $p < 0.01$). Among patients with anemia, there was a significant difference in WHO score associated with epoetin treatment only in the group of transplant recipients with mild anemia (WHO score with epoetin

Table 3: Immunosuppressive therapies

Immunosuppressants[a]	Total sample n = 4263	6 months n = 1003	1 years n = 960	3 years n = 1254	5 years n = 1046	Significance testing*
Steroids	3290 (84.5%)	829 (89.2%)	746 (83.8%)	958 (84.6%)	757 (80.2%)	$p < 0.01$
Cyclosporine	2518 (66.6%)	467 (52.6%)	436 (51.1%)	836 (75.0%)	779 (84.3%)	$p < 0.01$
Tacrolimus	1156 (31.3%)	430 (48.2%)	395 (47.6%)	226 (21.0%)	105 (11.8%)	$p < 0.01$
Mycophenolate mofetil (MMF)	1882 (50.2%)	575 (64.5%)	522 (60.8%)	562 (51.2%)	223 (24.8%)	$p < 0.01$
Azathioprine	1001 (26.9%)	169 (19.0%)	172 (20.5%)	307 (28.3%)	353 (38.7%)	$p < 0.01$
Sirolimus	54 (1.5%)	34 (3.9%)	10 (1.2%)	7 (0.7%)	3 (0.3%)	$p < 0.01$
Combinations[b]	Total sample n = 2973	6 months n = 753	1 years n = 664	3 years n = 873	5 years n = 683	Significance testing*
Cyclosporine/steroids	545 (18.3%)	90 (11.9%)	71 (10.7%)	141 (16.1%)	243 (35.5%)	$p < 0.01$
Tacrolimus/steroids	213 (7.1%)	53 (7.0%)	72 (10.8%)	57 (6.5%)	31 (4.5%)	$p < 0.01$
Cyclosporine/steroids/azathioprine	585 (19.6%)	89 (11.8%)	93 (14.0%)	191 (21.8%)	212 (31.0%)	$p < 0.01$
Tacrolimus/steroids/azathioprine	128 (4.3%)	32 (4.2%)	35 (5.3%)	41 (4.7%)	20 (2.9%)	p = NS
Cyclosporine/steroids/MMF	916 (30.7%)	236 (31.3%)	189 (28.4%)	353 (40.3%)	138 (20.2%)	$p < 0.01$
Tacrolimus/steroids/MMF	501 (16.8%)	241 (32.0%)	186 (28.0%)	57 (6.5%)	17 (2.5%)	$p < 0.01$
Steroids/MMF	85 (2.9%)	12 (1.6%)	18 (2.7%)	33 (3.8%)	22 (3.2%)	p = NS

*Chi-square: comparing proportions in four transplant cohorts.
[a]Categories are not mutually exclusive; [b]categories are mutually exclusive.

Table 4: Mean hemoglobin levels in the patients treated with various combinations of immunosuppressive therapies

Immunosuppressive therapies	Total sample (n = 4263) n	Hemoglobin (mean ± SD) (g/dL)
Cyclosporine/steroids	545	13.4 ± 2.0
Tacrolimus/steroids	213	13.5 ± 1.9
Cyclosporine/steroids/azathioprine	585	13.4 ± 1.9
Tacrolimus/steroids/azathioprine	128	13.0 ± 2.0
Cyclosporine/steroids/MMF	916	13.1 ± 1.9
Tacrolimus/steroids/MMF	501	13.0 ± 1.9
Steroids/MMF	85	12.6 ± 1.6

Table 5: Hemoglobin levels across various immunosuppressive regimens

All patients		n	Hemoglobin (mean ± SD) (g/dL)	Significance testing*
Tacrolimus and/or cyclosporine and/or steroids	With azathioprine	713	13.3 ± 1.9	p = NS
	Without azathioprine	758	13.4 ± 2.0	
Tacrolimus and/or cyclosporine and/or steroids	With MMF	1502	13.1 ± 1.9	$p < 0.01$
	Without MMF	758	13.4 ± 2.0	

*Independent samples *t*-test.

Table 6: Results of logistic regression of non-anemic and anemic patients

Variable	Odds ratio (OR)	95% CI of OR	p-value
Serum creatinine (> 2 mg/dL)	3.48	2.92–4.14	< 0.001
Age of donor (> 60 years)	1.41	1.16–172	< 0.001
ACE inhibitor or angiotensin II receptor antagonists	1.55	1.34–1.80	< 0.001
MMF or azathioprine	1.24	1.05–1.47	< 0.05
Polycystic kidney disease	0.70	0.56–0.88	< 0.01
Recent infection	1.36	1.13–1.64	< 0.001

Table 7: Results of logistic regression of the nonanemic and severely anemic patients

Variable	Odds ratio (OR)	95% CI of OR	p-value
Serum creatinine (> 2 mg/dL)	7.54	5.76–9.87	< 0.001
Age of donor (> 60 years)	0.97	0.68–1.39	NS
ACE inhibitor or angiotensin II receptor antagonists	1.58	1.27–2.07	< 0.001
MMF or azathioprine	1.22	0.90–1.65	NS
Polycystic kidney disease	0.55	0.35–0.87	< 0.001
Recent infection	2.12	1.58–2.85	< 0.001
Hepatitis	0.84	0.58–1.22	NS

0.5 ± 0.8, median 0, WHO score without epoetin 1.1 ± 0.9, median 1) ($p < 0.01$).

Discussion

Surveys are a valuable tool to collect data from a large study population. The main goal of the TRansplant European Survey on Anemia Management (TRESAM) was to create a large European database to document the prevalence and management of anemia. The primary objective of the survey was to document patient Hb levels to date and before transplantation, as well as to evaluate the current anemia treatment practices in transplant centers across Europe. This survey also presented an opportunity to gather additional information concerning the outcomes of kidney transplantation, comorbidities, clinical events, and medical treatments in transplant recipients. We need to keep in mind, however, that whereas surveys are valuable tools to document, they do not necessarily give us insight into the causes of findings.

Although the presence of renal anemia in renal transplant recipients is well known (3,10–12), figures on the exact prevalence of anemia after renal transplantation are extremely scarce. Only very recently have some data on a limited number of patients (n = 128) from two US centers been published (13). Despite its own limitations, the present descriptive survey is the first to document the prevalence and management of anemia in a large group of 4263 patients who received a kidney transplant 6 months to 5 years previously. The demographic data of both recipients and donors indicate that the patients included in this survey are a representative sample of the European transplant population. The prevalence of diabetic nephropathy as an underlying renal disease in this survey was much lower than the prevalence seen in other registries on renal replacement therapy, but this difference may be at least partially explained by the fact that patients who received a combined kidney–pancreas transplant were excluded from this survey. An additional explanation may be that a substantial number of patients come from Italy, Spain, and Portugal, where the incidence of both type 1 but especially type 2 diabetes mellitus is low. Although the proportion of type 2 diabetes patients who develop end-stage renal failure is growing in Europe as well, many of these patients develop end-stage renal failure at an older age, when they are considered as less optimal candidates for transplantation. The different diet habits, lower incidences of diabetes, hypertension and hyperlipidemia in Europe, particularly in the Mediterranean countries, may also explain the lower incidence of cardiovascular comorbidity as compared with the US. The survey revealed that a large proportion of the transplant recipients suffered from anemia. More than one-third of the transplant recipients in this survey was found to be anemic. This figure is comparable to the 26% of patients who were found to be anemic 5 years after transplantation in the paper of Yorgin et al. (13). Mean Hb at the time of transplantation was significantly higher in the cohorts of patients who had received transplants more recently than in the cohorts of patients who had received transplants 3 and 5 years ago. This suggests that anemia management in dialysis patients has improved over the last 5 years.

The restoration of endogenous erythropoietin secretion and the impact of this on the resolution of anemia after renal transplantation have been assessed in several studies. After an initial peak in erythropoietin levels within the first day after transplantation, the restoration of erythropoietin synthesis depends mostly on the recovery of graft function (14). Our findings indicate that 6 months after transplantation the mean Hb was approximately 13 g/dL, a level that no longer indicates anemia. Mean Hb after transplantation were similar in the four cohorts, indicating that Hb levels had reached a plateau after 6 months and that graft function had recovered.

Several factors may be related to the occurrence of anemia in renal transplant recipients. A successful renal allograft will not only restore the excretory functions of the kidney but also its endocrine functions through the restored synthesis of erythropoietin and active vitamin D. In many transplant recipients, graft function and erythropoietin synthesis are far less than optimal. Results of our survey show a strong correlation between Hb levels and graft function, expressed as serum creatinine and creatinine clearance. The majority of anemic patients had serum creatinine levels > 2 mg/dL, which indicates impaired kidney function.

Rejection episodes also affect the occurrence of anemia. Transplant recipients who had experienced one or more rejection episodes, or who had received a second or third graft, had lower Hb levels than recipients without rejection episodes or recipients of a first transplant. Although it has been shown that the onset of an acute rejection within the first month after transplantation completely abrogates the erythropoietic response (15), the correlation between Hb levels and previous rejections in our survey most likely results from the suboptimal kidney function in patients who had experienced several acute rejection episodes. More intensified immunosuppressive treatment to control the rejection or to prevent subsequent rejections, or the more frequent use of ACE inhibitors in these patients who are more prone to have higher blood pressure, may also play a role.

Donor age is another risk factor for anemia. In fact, in donors aged older than 60 years, the presence of anemia is significantly affected. As the use of donors aged more 60 years is increasing in Europe, donor age could have important clinical implications.

Several of the above-mentioned factors like kidney function, incidence of rejection and donor age may explain why the mean Hb level is lower in second- and third-transplant recipients than in first transplant recipients. Also the more widespread use of MMF in these patients may play a role.

Among the different immunosuppressive agents used after transplantation, the purine synthesis inhibitors azathioprine and MMF are best known to cause anemia (9). MMF selectively blocks the *de novo* or ribose-derived purine synthesis pathway, and is therefore not expected to have a major effect on the cell proliferation of bone marrow cells except on that of lymphocytes (16). Contrary to this expectation, a similar incidence of anemia was reported in the pivotal trials that compared MMF and azathioprine (17,18). In our survey, the lowest mean Hb levels were found in patients treated with combination therapy of MMF and steroids, and Hb levels were significantly lower in patients treated with immunosuppressant combinations including MMF than in those without MMF. In the present survey, the difference in mean Hb levels between patients treated with or without azathioprine did not reach statistical significance in the total patient sample. This may be because of the fact that low doses of azathioprine are used during combination therapy with the potent calcineurin inhibitors. When patients with poor kidney function (i.e. serum creatinine >2 mg/dL) were excluded from the analyses, the difference in mean Hb levels between patients treated with or without azathioprine reached statistical significance. In the past, depression of bone marrow proliferation as a result of azathioprine has been a frequent cause of transient anemia in renal transplant recipients. Macrocytosis was present in a majority of the patients treated with azathioprine. Selective erythroid toxicity of azathioprine is rare and poorly understood (19).

Other medications used after transplantation with possible erythrotoxic effects include the ACE inhibitors. In our survey, no significant difference could be found in Hb levels between patients treated with ACE inhibitors and those not given ACE inhibitors. Still, the associative regression analysis showed that the use of ACE inhibitors or angiotensin II receptor antagonists was associated with a higher likelihood of anemia. One possible explanation may be that ACE inhibitors are not only given as antihypertensives, but also to correct post-transplant erythrocytosis. The more recent angiotensin II receptor antagonists are still less popular as antierythrocytosis drugs, which may explain the lower Hb levels seen in the patients treated with these drugs. As angiotensin II receptor antagonists were introduced more recently, it may be that other factors like the more frequent use of MMF or the use of older donors may at least in part also explain the lower Hb in these patients.

Anemia in kidney transplant recipients may negatively affect long-term outcome. Anemia in patients who undergo hemodialysis has been linked to the development of left ventricular hypertrophy, and is therefore considered to be a major contributor to cardiovascular risk (4,5). Anemia may also be a major contributor to cardiovascular risk in post-transplant patients, which is particularly worrying because cardiovascular events are known to be the main cause of death in post-transplant recipients (6). This survey revealed that many post-transplant patients (38.6%) are anemic but only few receive adequate anemia treatment. Even transplant recipients with severe anemia received epoetin in only 17.8% of cases. In pretransplant patients, observational studies and clinical trials indicate that treatment of anemia of renal failure with epoetin improves left ventricular structure and function, increases cardiac output, and improves quality of life (4,5). Whether the same holds true for renal transplant recipients with persistent or recurrent anemia is still to be proven. In addition, neither for dialysis patients nor for predialysis patients, a consensus has been reached on the optimal target Hb with epoetin therapy. Should all anemic transplant recipients be treated with epoetin in an attempt to normalize their Hb, or should treatment be reserved only for those who are severely anemic? Will epoetin therapy in transplant recipients be as effective as in nontransplanted patients? Several reports of small groups of patients have shown that epoetin is as effective in renal transplant recipients as in dialysis patients (20–22). However, epoetin resistance in transplant recipients, probably related to the inflammatory syndrome of chronic rejection, has been reported as well (23). The fact that in our survey the mean Hb level in patients receiving epoetin was significantly lower than in patients not receiving epoetin is in our opinion more a result of the design of the survey than an indication of erythropoietin resistance. Only prospective interventional

studies in anemic renal transplant recipients will be able to better answer these questions.

Acknowledgment

This study was sponsored by Ortho Biotech, a division of Janssen-Cilag.

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