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Impact of pre-transplant anaemia correction and erythropoietin resistance on long-term graft survival

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Abstract

Background. This study investigated whether recombinant human erythropoietin (rHuEPO)-hyporesponsive anaemia before transplantation is associated with a poorer graft outcome and lower patient survival.

Methods. A total of 15 051 kidney transplant recipients, with a minimum follow-up of 1 year, were stratified as either rHuEPO hyporesponsive or rHuEPO responsive (using a threshold rHuEPO-treated haemoglobin level of 11 g/dl). They were followed for a median of 24 months. Outcomes included times from transplantation to graft failure (including patient death), return to dialysis or pre-emptive re-transplantation, and death with a functioning graft.

Results. The cumulative incidence of graft failure was 50% for rHuEPO-hyporesponsive patients, compared with 41.7% for rHuEPO responders ($P = 0.0091$). Among rHuEPO-hyporesponsive patients, 41.7% returned to dialysis or underwent a pre-emptive re-transplantation, compared with 32% of rHuEPO responders ($P = 0.0091$). Death with a functioning graft occurred in 16.9% of rHuEPO-hyporesponsive and in 15% of rHuEPO-responsive patients ($P = 0.3949$).

Conclusions. The results showed higher mortality and higher incidence of graft failure at 5 years for rHuEPO-hyporesponsive patients. It is unclear whether anaemia treatment *per se* or treatment of more severe co-morbidity resulting in hyporesponsiveness to anaemia treatment may be causally linked to reduced renal transplant outcomes.

Keywords: aggressive treatment; anaemia; graft failure; patient survival; post-transplant patients; rHuEPO hyporesponsiveness

Introduction

Cardiovascular disease is the main cause of mortality in renal transplant patients [1,2]. In addition to traditional risk factors such as hypertension, diabetes, hyperlipidaemia and cigarette smoking, a number of other factors may contribute to the development of cardiovascular disease after renal transplantation. Among them, attention has been focused on anaemia [3–5].

The introduction of recombinant human erythropoietin (rHuEPO) has been a cornerstone in the treatment of anaemia associated with chronic kidney disease or renal transplantation. Most patients show an excellent response to rHuEPO, reaching target haemoglobin (Hb) levels. However, some patients fail to respond to rHuEPO.

A number of factors may cause a lack of response. Iron deficiency, hyperparathyroidism and/or aluminium accumulation have been shown to impair the responsiveness to rHuEPO [6]. An inadequate response can also be caused by an infectious or inflammatory status as a consequence of the release of pro-inflammatory cytokines that inhibit erythropoiesis [7]. In this regard, it has been demonstrated that transplant recipients have an early gene expression of inflammatory cytokines [8] that represents a high inflammatory burden with a potentially negative impact on graft outcome. Moreover, in a retrospective study, Lietz *et al*. [9] demonstrated that the use of rHuEPO prior to transplantation was associated with a decline in late post-transplant alloreactivity and improved late renal graft survival. These data would suggest that persistence of anaemia in spite of adequate rHuEPO administration might expose transplant recipients not only to cardiovascular risk but also to graft dysfunction.

Persistent and erythropoietin-hyporesponsive anaemia before transplantation may represent a state of inflammatory burden to the transplant patient.

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Therefore, we chose to investigate whether rHuEPO-hyporesponsive anaemia before transplantation is actually associated with a poor graft outcome and lower patient survival.

Patients and methods

Inclusion criteria

Kidney transplant recipients included in the Medicare Renal Beneficiary Utilization System (REBUS)/UNOS database from January 1995 to December 2002, with a minimum follow-up of 1 year, were considered for the study.

Definitions

Erythropoietin hyporesponsiveness was defined as a weekly dose of rHuEPO >300 U/kg/week without an adequate rise in Hb [10]. The rHuEPO/Hb ratio was used to assess the correction of anaemia.

Patients were divided on the basis of their pre-transplant anaemia correction into rHuEPO-hyporesponsive patients [rHuEPO/Hb below median (11 g/dl)] and rHuEPO responders (rHuEPO/Hb above median). Data on cold ischaemia time were collected. Delayed graft function was defined as the need for dialysis after transplantation.

Statistical analysis

Patients were followed for a median of 24 months (25th percentile 9 months; 75th percentile 43 months) until December 31, 2002. Outcomes investigated were graft failure (including patient death), return to dialysis or pre-emptive re-transplantation, and death with a functioning graft. Times from transplantation to each of the three possible outcomes were modelled using Kaplan–Meier analyses, and failure rates were modelled using Poisson regression. Poisson regression models were adjusted for procedure type (kidney alone *vs* kidney–pancreas), age, gender, race, primary cause of disease, total in-patient days in the 3 month period before transplantation, cause of hospitalization in the 3 month period before hospitalization, donor type, total time on dialysis, panel reactive antibodies (PRA) (>50%), human leukocyte antigen (HLA) mismatches and body mass index. All analyses were conducting using SAS version 9.1 (Cary, NC).

Results

Table 1 shows the demographic and main clinical characteristics of the patients and demonstrates that there were no clinically relevant differences between rHuEPO-hyporesponsive and rHuEPO-responder patients. Between January 1995 and December 2002, 109 724 patients were transplanted, of whom 104 011 were aged >17 years at the time of transplantation. Of these, 91 966 were recipients of a first transplant and 17 395 were on long-term haemodialysis treatment. After adjusting for the inclusion criteria, 13.7% of patients were selected, and the final sample included 15 051 patients (Table 2).

Before transplantation, a total of 1454 patients received a dose of rHuEPO that was higher than 300 U/kg/week: 348 patients showed constantly low Hb levels while 1106 achieved the Hb target (>11 g/dl) and were defined as rHuEPO responders.

Table 1. Demographic and main clinical characteristics of the patients

	rHuEPO-hyporesponsive patients	rHuEPO responders
No. of patients	348	14 703
Age (years)*†	46 (14)	48 (14)
Male*	52%	61%
Race*		
White	56%	64%
Black	34%	30%
Asian	3%	4%
Other	2%	2%
Basic disease*		
Diabetes mellitus	31%	33%
Hypertension	24%	23%
Glomerulonephritis	18%	21%
Autosomal polycystic kidney disease	3%	5%
Other	24%	17%
Dialysis time (months)	36 (26)	35 (24)
Haemodialysis/peritoneal dialysis	All HD	All HD
HBV (active or antibodies)/ HCV status	9%/6%	9%/5%
Living donor*	28%	23%
Kidney–pancreas recipient	5%	7%
PRA (>50%)	4%	3%
HLA + B + DR mm	3.3 (1.8)	3.3 (1.8)
Cold ischaemia time (HRS)	15 (12)	15 (11)
Early acute rejection	8%	7%
Delayed graft function*	26%	22%

†Where appropriate, data are expressed as the mean (SD).
*$P < 0.05$.

Table 2. Cohort construction

Criterion	*n*	% of previous figure
All renal transplants, 1995–2002	109 724	100.0
Age >17 years at time of transplant	104 011	94.8
First transplant	91 966	88.4
Medicare primary pay in the month immediately prior to transplant	40 135	43.6
Medicare primary pay for the 3 consecutive calendar months prior to the month of transplant	39 381	98.1
At least two monthly rHuEPO bills in those 3 months	18 685	47.4
Primarily haemodialysis in the 3 months	17 395	93.1
Monthly rHuEPO bills in all 3 months	15 051	86.5
Final sample: 15 051 (13.7% of all transplants, 1995–2002)		

The cumulative incidence of graft failure was 50% at 60 months for rHuEPO-hyporesponsive patients, compared with 41.7% for rHuEPO responders ($P = 0.0091$) (Figure 1). The graft failure rate per 100 patients per year was 9.71 for rHuEPO responders, compared with 11.91 for rHuEPO-hyporesponsive subjects—hazard ratio 1.23 ($P = 0.0338$) (Figure 2). Among rHuEPO-hyporesponsive patients, 41.7% returned to dialysis or underwent a pre-emptive re-transplantation; this compared with 32% of the rHuEPO responders ($P = 0.0091$). According to Poisson regression analysis, return to dialysis or pre-emptive re-transplantation was 5.85 per 100 patients per year for rHuEPO responders and 7.8 for rHuEPO-hyporesponsive subjects, respectively—hazard ratio 1.26.

Death with a functioning graft occurred in 16.9% of rHuEPO-hyporesponsive patients and in 15% of rHuEPO responders ($P = 0.3949$)—hazard ratio 1.17 ($P = 0.3647$) (Figures 3 and 4).

Discussion

Anaemia is not an infrequent disorder in renal transplant recipients. One European survey reported that 38.6% of renal transplant patients were anaemic and 8.5% had severe anaemia [11]. Renal graft dysfunction, not surprisingly, is also significantly correlated with anaemia. It is unclear if this association is secondary to reduced erythropoietin-releasing kidney tissue or if this represents an inflammatory marker in those with reduced allograft kidney function. Other sources of anaemia in the post-transplant period include the use of angiotensin-converting enzyme (ACE) inhibitors, mycophenolate mofetil or azathioprine [11]. The clinical manifestations of anaemia may not only impair the quality of life—being responsible for fatigue, dyspnoea, palpitations and other symptoms—but can also represent an independent risk factor for cardiovascular disease, as shown both in general populations [12] and in dialysis patients [13–15]. As anaemia may also impact negatively on the long-term outcome of patients and grafts, it should be considered as a major problem in renal transplant recipients [16].

It has been suggested that correction of anaemia with rHuEPO should also be extended to transplant patients [16]. This is because erythropoietin may be of benefit in patients with chronic allograft dysfunction, as it can slow the rate of loss of function over time [17]. However, the number of transplant patients treated with rHuEPO is low, as reported by a large retrospective European survey [11] and confirmed by the low percentage of patients receiving rHuEPO in published US data.

In the current study, we investigated whether the presence of erythropoietin hyporesponsiveness—defined as a weekly rHuEPO dose >300 U/kg without reaching a target Hb of 11 g/dl before transplantation—can affect patient and/or graft survival after transplantation. Our results showed a statistically significantly higher mortality and higher incidence of graft failure at 5 years for rHuEPO-hyporesponsive patients. The elevated mortality in rHuEPO-hyporesponsive patients might be explained by left ventricular hypertrophy, a well-known anaemia-related risk factor for cardiovascular disease [18]. However, it is likely that anaemia also contributed to mortality by exposing patients to a milieu of inflammatory cytokines and increased oxidative stress.

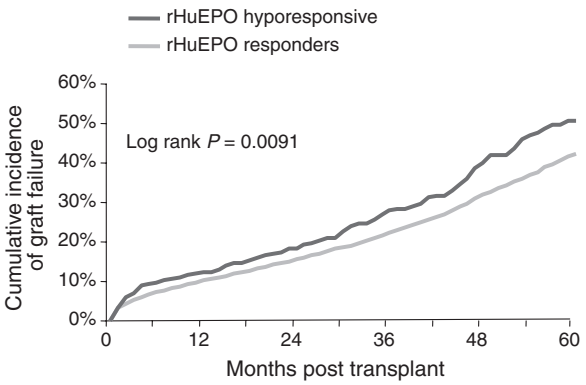

Fig. 1. Graft survival, Kaplan–Meier analysis.

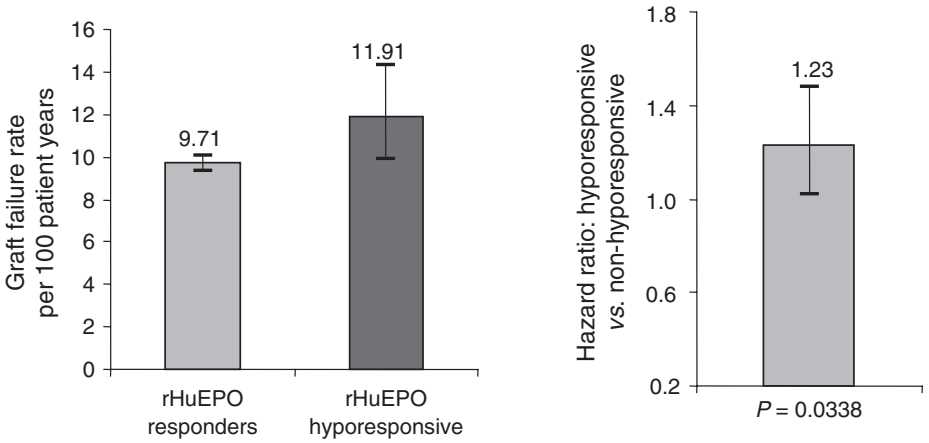

Fig. 2. Results of Poisson regression analysis (adjusted) for graft failure.

The association of malnutrition, inflammation and atherosclerosis (MIA) in end-stage renal disease has led to the definition of the MIA syndrome: this is characterized by high levels of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor-α (TNF-α). [19]. This pro-inflammatory pattern persists for at least a few weeks after transplantation, particularly in erythropoietin-hyporesponsive patients in whom rHuEPO therapy may not be able to change the chronic inflammatory allograft pattern [7]. In a recent paper, Hirayama *et al*. investigated the relationship between anaemia resistant to rHuEPO therapy and oxidative stress in haemodialysis patients [20]. The authors found that there is reduced serum hydroxyl radical scavenging activity in erythropoietin-hyporesponsive patients demonstrated by increased intra-erythrocyte levels of thiobarbituric acid-reactive substances. These results would indicate that increased lipid peroxidation is one of the causes of erythropoietin-hyporesponsive anaemia.

Renal transplant patients have a pattern of increased oxidative stress that may be balanced by an enhancement of the anti-oxidant mechanisms in non-anaemic patients. Similarly, an increased oxidative pattern occurs in anaemic patients, as demonstrated by the direct correlation between haematocrit and thiol groups [21]. Correction of anaemia, improving the renal oxygen delivery, could therefore ameliorate the oxidative stress. The combination of pro-inflammatory pattern and increased oxidative stress could also be explained, at least partially, by the unfavourable impact of resistance to rHuEPO on graft survival. It is also possible that, in these patients, changes in immunosuppression occur more frequently, because of anaemia and patient fragility. This may result in subclinical rejection and poorer graft survival [22,23].

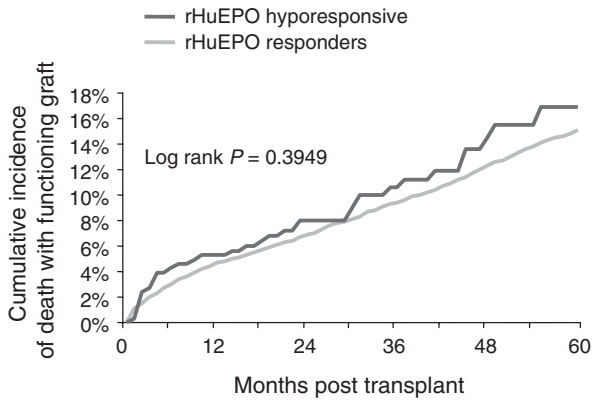

Fig. 3. Patient survival, Kaplan–Meier analysis.

There are important limitations to consider in this study of graft survival and its association with rHuEPO hyporesponsiveness. The data set from Medicare represents only ~60% of the transplanted population. The non-Medicare population may have different outcomes, based on the younger cohorts in the employer group-healthcare plans. Unfortunately, there are few data available from the non-Medicare population, thereby limiting the analysis to the Medicare group. There were no cytokine level data available for the US transplant population on a national level. For this reason, we chose to use, as a surrogate for the inflammatory load in the pre-transplant period, the rHuEPO dose. It would have been better to include the breadth of inflammatory markers, but this information is not available on a large national sample of patients receiving a kidney transplant. Lastly, the associations noted in this study do not imply causality between rHuEPO hyporesponsiveness and reduced graft survival. rHuEPO hyporesponsiveness may simply represent the degree of inflammatory burden, which is a predictor of graft failure. Further studies relating these confounded relationships are needed.

In summary, erythropoietin resistance can affect ~30% of end-stage renal disease patients on the waiting list for transplantation. These patients may experience reduced graft survival as well as shorter life span. It is unclear whether the rHuEPO dose or the level of Hb in the pre-transplant period plays a causal role. These considerations underscore the need for prospective studies in order to confirm the inferior results in this particular population and to clarify whether a

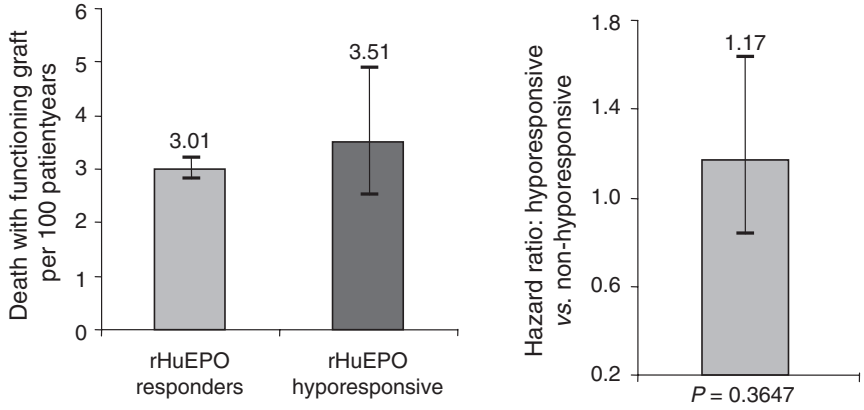

Fig. 4. Results of Poisson regression analysis (adjusted) for death with functioning graft.

more aggressive treatment of anaemia before and after transplantation may improve the prognosis for patients.

Conflict of interest statement. None declared.

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