A prospective study of anaemia and long-term outcomes in kidney transplant recipients

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Abstract

Background. Anaemia is prevalent in kidney transplant recipients (KTR), and only few KTR with anaemia receive treatment with erythropoietin. Some have claimed that this undertreatment might contribute to suboptimal outcomes such as mortality and cardiovascular events in these patients. However, no evidence is currently available that anaemia is actually associated with such risks in KTR.

Methods. We merged two cohorts of KTR to study the associations between anaemia and two outcomes: all-cause mortality and kidney allograft loss. Detailed information on the demographic and clinical characteristics of these 825 patients was available at baseline. As recommended by the American Society of Transplantation, anaemia was considered present if the haemoglobin concentration was \( \leq 13 \) g/dl in men or \( \leq 12 \) g/dl in women. Patients were followed using the Austrian Dialysis and Transplant Registry.

Results. After 8.2 years of follow-up, 251 patients died and 401 allografts were lost. In multivariate analyses, anaemia was not associated with all-cause mortality (HR: 1.08; 95% CI: 0.80–1.45), but it was associated with 25% greater risk of allograft loss (HR: 1.25; 95% CI: 1.02–1.59). This association was even more pronounced in death-censored analyses. Analyses using haemoglobin as a continuous variable or in categories also found no association with mortality.

Conclusions. Anaemia may not be associated with mortality in KTR. In light of the recent findings of increased mortality in chronic kidney disease patients with higher haemoglobin concentration, further evidence is needed to guide clinicians in the treatment of anaemia in these patients.

Keywords: anaemia; allograft survival; kidney transplantation; mortality

Introduction

Several recent studies of kidney transplant recipients (KTR) have revealed that anaemia is quite prevalent in this patient population. Depending on the definition of anaemia and whether haemoglobin concentration or haematocrit was measured, the prevalence of anaemia in KTR was estimated to be between 20 and 40% [1–6]. A secondary finding of these studies was that only a minority of patients received treatment with recombinant human erythropoietin (rh-Epo), even if they were anaemic. Several authors explicitly or implicitly concluded that anaemia in KTR was undertreated and that more aggressive treatment of anaemia could lead to better outcomes in these patients. Little is known, however, about the association between anaemia and outcomes in KTR such as mortality, cardiovascular risk and kidney allograft loss. Only if anaemia were associated with adverse outcomes in KTR would an assessment of ‘undertreatment’ be legitimate.

Studies of the outcomes associated with anaemia in KTR are scarce. We recently published a prospective cohort study of 438 KTR and found that haemoglobin concentrations were not associated with all-cause mortality or kidney allograft loss after \( > 7 \) years of follow up [7]. In contrast, the percentage of hypochromic red blood cells (%HRBC), a marker for iron availability and utilization [8], was inversely associated with mortality risk. We acknowledged, however, the possibility that our failure to detect any associations between haemoglobin concentrations
and the study outcomes was a consequence of limited power.

Therefore, we designed the present study. In order to increase statistical power, we merged two well-studied cohorts of KTR. In addition to testing the association between haemoglobin concentrations and outcomes, we also sought to assess the presence of anaemia, as defined by the American Society of Transplantation [9], as a main study exposure.

Subjects and methods

Study population

We merged the patient-level data of two cohorts of KTR from the Vienna General Hospital. One cohort of 438 stable KTR was assembled in 1995 to study anaemia and iron status in KTR, and a complete follow-up is available for these patients [2,7,10]. The second cohort was assembled in late 1996–98 to study the prevalence and correlates of homocysteine and included 733 KTR [11]. Complete baseline and follow-up information was available for 710 of these patients [12]. All patients consented to being included in these studies. Patients who were enrolled in both cohorts contributed person time starting with enrollment in the earlier study. During the baseline visit of both studies, we ascertained each participant’s age, gender (all patients were White/Caucasian), weight, height, underlying native kidney disease, time since last kidney transplantation and how many such procedures they had undergone previously. Each patient’s body mass index (BMI) was calculated as the weight in kilograms divided by the squared height in metres. We noted the exact immunosuppressant regimen at that time. Blood was drawn during the enrollment visit and blood chemistry values were determined immediately at a single laboratory using standard methods: serum-creatinine, C-reactive protein and serum-iron. We calculated each patient’s creatinine clearance (Ccr) using the Cockcroft–Gault formula and standardized to a body surface area of 1.73 m2 [13]. Haemoglobin concentrations were used to assess whether a patient was anaemic; following the definition recommended by the American Society of Transplantation [9], anaemia was considered present if the haemoglobin concentration was >12 g/dl in women or >13 g/dl in men, respectively.

Study follow-up

From the day of the baseline visit, patients were followed longitudinally using the Austrian Dialysis and Transplant Registry (OeDTR) and the registry of the Eurotransplant Foundation, the joint organ procurement agency for Austria, Belgium, Germany, Luxemburg, The Netherlands and Slovenia. The OeDTR routinely collects longitudinal information on all dialysis patients and KTR residing in Austria. Follow-up in this database has been 100% complete for many years and reliable information on timing and occurrence of patient death and modality switches, such as re-initiation of maintenance dialysis after kidney graft failure, is available for study. From the Eurotransplant Foundation database, we obtained information on the organ donor (donor age, gender, living vs cadaveric donor) and on the specific circumstances of the transplantation procedure [cold ischaemia time, number and type of human leucocyte antigen (HLA)-mismatches and recipient panel reactive antibody (PRA)-titre].

Statistical analyses

All statistical analyses used the SAS for Windows statistical software package (release 8.2; The SAS Corporation, Inc., Cary, NC). Baseline characteristics were compared between KTR with or without anaemia. We then built univariate and multivariate Cox proportional hazard models to describe the crude and independent relationships between the main exposure variables and the outcomes of interest [14]. These were all-cause mortality and kidney allograft loss, which was defined as the composite endpoint of patient death and re-initiation of maintenance dialysis. We also conducted analyses that used re-initiation of maintenance dialysis as the outcome, and death as a censoring rather than an event indicator (death-censored graft failure). Hazard ratios (HRs) were used as the measure of association and provided together with the corresponding 95% confidence interval (CI).

We first explored the relationship between increasing haemoglobin concentrations (>10–11, >11–12, >12–13, and >13 g/dl) and the outcomes of study using ≤10 g/dl as the reference group. In addition, we presented selected bi-variate and tri-variate models to illustrate the influence of important confounders such as age and/or estimated creatinine clearance. For all multivariate analyses, we used automated stepwise model selection procedures that only included variables below a multivariate P < 0.20 in the outcome model. From there, we tested whether any of the remaining variables confounded the association between the main exposure variables and the outcomes of interest. We regarded a variable a marginal confounder if its inclusion in the selected model changed the effect estimate of interest by >10%, in which case the variable was included regardless of any significance threshold. The same algorithm was used to study the associations with presence of anaemia (dichotomous). We also tested for the presence of any interactions between the covariates and the main exposure variables, but found no indication for the presence of effect modification.

Results

After merging the two databases, we obtained a joint cohort of 825 KTR. At baseline, 339 (41.1%) patients were anaemic, while 486 (58.9%) were above the gender-specific threshold levels. Crude comparisons between these groups revealed that anaemic patients were younger, had a lower BMI and their kidney function was more impaired (Table 1). Further, KTR with anaemia had a lower serum iron concentration and were more likely to have undergone repeat kidney transplantation (Table 2). Underlying kidney disease, immunosuppressive regimen and cold ischemia time were also different between these groups. A detailed description of the study population, their donors and the actual transplant procedure is provided in Tables 1
Anaemia and long-term outcomes in kidney transplantation

Table 1. Baseline characteristics of 825 kidney transplant recipients

<table>
<thead>
<tr>
<th>Variable n (%) or mean (±SD)</th>
<th>Anaemia (n = 339;41.1%)</th>
<th>No anaemia (n = 486;58.9%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (years)</td>
<td>49.1 (±13.9)</td>
<td>53.4 (±12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient gender (male)</td>
<td>206 (60.8%)</td>
<td>285 (58.6%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Time since transplantation (years)</td>
<td>4.3 (±4.1)</td>
<td>4.8 (±4.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.0 (±1.0)</td>
<td>1.5 (±0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>46.8 (±17.9)</td>
<td>58.4 (±17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 (±4.0)</td>
<td>25.8 (±4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum iron (mg/dl)</td>
<td>75.8 (±32.1)</td>
<td>84.2 (±34.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>≤0.5</td>
<td>278 (82.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5–1.0</td>
<td>25 (7.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1.0</td>
<td>36 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Underlying renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>16 (4.7%)</td>
<td>37 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>127 (37.5%)</td>
<td>141 (29.0%)</td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>33 (9.7%)</td>
<td>54 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>35 (10.3%)</td>
<td>75 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Various, other, specified</td>
<td>37 (10.9%)</td>
<td>54 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Unspecified/unknown</td>
<td>91 (26.8%)</td>
<td>125 (25.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immunosuppressive regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA + Corticosteroid</td>
<td>177 (52.2%)</td>
<td>217 (44.7%)</td>
<td></td>
</tr>
<tr>
<td>CsA + Corticosteroid + Azathioprin</td>
<td>61 (18.0%)</td>
<td>157 (32.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>101 (29.8%)</td>
<td>112 (23.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CsA, cyclosporine A.

Table 2. Transplantation-specific characteristics of study population

<table>
<thead>
<tr>
<th>Variable n (%) or mean (±SD)</th>
<th>Anaemia (n = 339;41.1%)</th>
<th>No anaemia (n = 486;58.9%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous kidney transplants</td>
<td>257 (75.8%)</td>
<td>414 (85.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>66 (19.5%)</td>
<td>64 (13.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (4.7%)</td>
<td>8 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor organ type (living vs cadaveric)</td>
<td>22 (6.5%)</td>
<td>20 (4.1%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Donor age (in years)</td>
<td>39.6 (± 14.7)</td>
<td>37.5 (± 15.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Donor gender (male)</td>
<td>218 (64.3%)</td>
<td>320 (65.8%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Number of HLA-mismatches</td>
<td>2.3 (± 1.2)</td>
<td>2.1 (± 1.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cold ischaemia time (in hours)</td>
<td>19.8 (± 7.8)</td>
<td>21.3 (± 7.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Panel reactive antibody titer (&gt;50% vs ≤50%)</td>
<td>24 (7.1%)</td>
<td>33 (6.8%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

HLA, human leucocyte antigen.

and 2. Table 3 shows the overall and gender-specific distribution of patients by category of haemoglobin concentration.

The cohort was followed-up for a median of 8.2 years. After 5906 person-years, 251 patients died (crude mortality rate = 42.5/1000 person-years) and after 5138 person-years of follow-up, 401 kidney allografts were lost (crude rate of allograft loss = 78.0/1000 person-years).

Analyses of kidney transplant recipient mortality

Compared with a haemoglobin concentration of ≤10 g/dl, the univariate HRs by ascending haemoglobin concentration were 0.70 (95% CI: 0.41–1.21; Hb >10–11 g/dl), 0.59 (95% CI: 0.36–0.99; Hb >11–12 g/dl), 0.68 (95% CI: 0.42–1.11; Hb >12–13 g/dl) and 0.64 (95% CI: 0.41–1.00; Hb >13 g/dl), respectively (Table 4). As indicated in Table 4, age and Ccr were important confounders into opposite directions. From the multivariate model, we found no association between haemoglobin concentrations and all-cause mortality; compared with Hb ≤10 g/dl, the respective adjusted HRs were 0.80 (95% CI: 0.45–1.42; Hb >10–11 g/dl), 0.78 (95% CI: 0.45–1.34; Hb >11–12 g/dl), 0.80 (95% CI: 0.46–1.40; Hb >12–13 g/dl) and 0.76 (95% CI: 0.44–1.31; Hb >13 g/dl; Table 4). The likelihood ratio test failed to indicate that the model including the hemoglobin categories contributed significant information beyond the more parsimonious model (P = 0.90).

Next, we examined the association between anaemia (using the gender-specific Hb thresholds) and mortality in these KTR. From the univariate analysis, we did not find an association (HR = 1.05;
95% CI: 0.82–1.35; Table 6). Separately including age and C\textsubscript{cr} into the model again revealed that these factors were powerful confounders of the univariate association. The HR from the full model, however, did not materially differ from the univariate finding (HR = 1.08; 95% CI: 0.80–1.45); no association was detected between anaemia and all-cause mortality in these KTR.

We confirmed the robustness of these results in several sensitivity analyses. Specifically, the results remained materially unchanged whether we included serum iron in the model or whether we restricted the analysis to patients with C\textsubscript{cr} > 20 ml/min/1.73 m\textsuperscript{2}. Further, patients with Hb < 10 g/dl vs all other patients (Hb > 10 g/dl) did not differ in mortality risk (HR = 1.28; 95% CI: 0.79–2.06). Finally, using haemoglobin as a continuous variable did not yield a significant association with mortality either (HR for each 1 g/dl increase in Hb concentration = 0.98; 95% CI: 0.90–1.07).

### Analyses of kidney allograft loss

Compared with a haemoglobin concentration of ≤ 10 g/dl, the univariate HRs by ascending haemoglobin concentration were 0.73 (95% CI: 0.49–1.08; Hb > 10–11 g/dl), 0.50 (95% CI: 0.34–0.74; Hb > 11–12 g/dl), 0.45 (95% CI: 0.31–0.65; Hb > 12–13 g/dl) and 0.35 (95% CI: 0.25–0.50; Hb > 13 g/dl), respectively (Table 5). Recipient age was not a confounder, but inclusion of C\textsubscript{cr} in the model yielded substantially attenuated HRs. From the multivariate model, we found a trend towards lower rates of kidney allograft loss in patients with higher haemoglobin concentrations; compared with Hb ≤ 10 g/dl, the respective adjusted HRs were 1.02 (95% CI: 0.67–1.57; Hb > 10–11 g/dl), 0.83 (95% CI: 0.55–1.26; Hb > 11–12 g/dl), 0.79 (95% CI: 0.52–1.22; Hb > 12–13 g/dl) and 0.66 (95% CI: 0.43–1.02; Hb > 13 g/dl; Table 5).

As mentioned, the likelihood ratio test comparing the models with vs without haemoglobin categories was not significant (P = 0.13). When we restricted the analysis to patients with C\textsubscript{cr} > 20 ml/min/1.73 m\textsuperscript{2}, the findings were even more pronounced and a comparison between KTR with Hb ≤ 10 g/dl and those with Hb > 13 g/dl revealed a 42% lower rate of allograft loss in those latter (HR = 0.58; 95% CI: 0.37–0.91; Table 4).

The univariate analysis of anaemia and kidney allograft loss revealed a substantially greater risk
of that outcome in patients who were anaemic (HR = 1.67; 95% CI: 1.38–2.04; Table 7). Even after multivariate adjustments, KTR with anaemia at baseline had a 27% greater risk of kidney allograft loss (HR = 1.27; 95% CI: 1.02–1.59; Table 5). This finding remained robust even after exclusion of patients whose kidney function was already severely impaired (Ccr ≤ 20 ml/min/1.73 m²).

When conducting analyses of allograft loss (return to dialysis) where death was used as a censoring indicator rather than an outcome, the results were very similar to the ones obtained from the combined endpoint above. From univariate analyses, patients with anaemia had a 2.5-fold risk of death-censored allograft loss (HR = 2.45; 95% CI: 1.89–3.18). This association was substantially attenuated after multivariate adjustment; patients with anaemia had a 38% greater rate of death-censored allograft loss compared with patients without anaemia at baseline (HR = 1.38; 95% CI: 1.02–1.86). These results were identical after exclusion of KTR with Ccr ≤ 20 ml/min/1.73 m².

### Discussion

This is the largest cohort study to date of the putative association between anaemia and important outcomes in KTR such as mortality and kidney allograft loss. After > 8 years of follow-up, we found no association between haemoglobin concentrations or anaemia and all-cause mortality. In contrast, patients without
anaemia or with greater haemoglobin concentrations appeared to have lower rates of kidney-allograft loss, defined as the combined endpoint of return to dialysis and death. Anaemia, defined as a haemoglobin concentration ≤12 g/dl in women or ≤13 g/dl in men [9], was associated with a 25% increased risk of death and return to dialysis combined, and a 38% increased risk of allograft loss when censoring for death. These findings arose from multivariate models that carefully controlled a large number of potential confounders.

The finding that anaemia was not associated with all-cause mortality confirms recent findings in heart transplant patients [15] and our earlier study of 438 KTR [7]. While we speculated that limited power in that study could have contributed to the finding of no association, the present study contains nearly twice as many patients and longer follow-up. Interestingly, a study of 638 KTR who were free from clinically evident heart disease at 1 year after transplantation found lower haemoglobin concentrations to be associated with a greater incidence of congestive heart disease and cardiovascular disease [16]. Unfortunately, comprehensive multivariate adjustment was not possible in this study due to the relatively small number of outcomes observed. It may also be inappropriate to compare the results from this study of incident KTR with ours of prevalent KTR. Our results are in stark contrast with findings from observational studies in patients on dialysis. In several of these studies, lower haemoglobin levels or haematocrit have been found to be associated with greater mortality [17,18]. It is possible that these studies did not include certain factors that might be important confounders of these associations, namely indicators of inflammation and iron availability, amongst others. This notion is supported by the finding that patients with lower rh-Epo dose experienced superior long-term outcomes compared with patients who required higher doses of the hormone [19]. Thus, haemoglobin concentration, anaemia or required rh-Epo dose might simply be indicators for complex underlying mechanisms of disease that are, in turn, associated with adverse outcomes. A study that randomized dialysis patients with congestive heart failure to a treatment target haematocrit of 42 and 30%, respectively, revealed a trend towards greater mortality in the high-haematocrit group [20]. More relevant to our study of anaemia in KTR are the recently presented results from the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, in which patients with chronic kidney disease were randomized to a treatment target haemoglobin concentration of 11.3 vs 13.5 g/dl, respectively. [Ajay K. Singh, MD; Presentation at the 2006 Clinical Meetings of the National Kidney Foundation, 20 April 2006, Chicago, IL] Patients in the higher target haemoglobin group had a significantly greater mortality and the study was halted early. Thus, these results indirectly support our findings in that they also refute the widely held belief that higher haemoglobin concentrations are better.

In this study, we find an association between increased allograft loss and lower haemoglobin. Although we did not specifically investigate the use of rh-Epo in this study, given the time period for the collection of the data it is likely that very few, if any, patients were treated with rh-Epo. A recent study of 166 KTR has suggested that rh-Epo therapy may be associated with a more moderate decline in allograft function [21], but censoring on a correlate of the study end point renders its validity questionable. The direction of the association between anaemia and graft function is not clear from our study. Despite the fact that we factored in one measure of renal function (C_crr), it is possible that the full impact of erythropoietin production by a failing graft was not captured by measuring this parameter. One possible mechanism may be an inflammatory response in the form of rejection. The incidence of subclinical rejection in KTR treated with a similar immunosuppressive regimen was 15–43% in protocol biopsies taken at various time points between 1 and 6 months post transplant [22]. A recent study has shown that an ‘erythropoiesis cluster’ of 11 genes involved in haemoglobin transcription and synthesis, iron and folate binding and transport are down-regulated in the presence of acute allograft rejection [23]. Another study of patients with failed allografts who return to dialysis, compared groups of patients who were nephrectomized with those who were not, and found that resection of failed transplants in symptomatic patients is associated with higher haemoglobins, less rh-Epo resistance and amelioration of markers of chronic inflammation when compared with patients who were not nephrectomized [24]. These studies would appear to support the notion that rejection, whether clinical or subclinical, could cause a decrease in haemoglobin levels through erythropoietin resistance. Thus, anaemia would be a surrogate of chronic rejection and would reflect a state of chronic inflammation due to a failed graft. Alternatively, lower haemoglobin might demarcate the presence of other risk factors potentially injurious to the allograft.

This study has certain limitations. We acknowledge the hypothesis-generating nature of this study, and its findings will need to be validated in other settings. The study inclusion of prevalent rather than incident patients allows for the presence of time-related biases, mainly survival bias. We deem this to be unlikely, which is supported by our failure to formally detect any violations of the proportionality assumption of the hazards in these Cox models. Further, the present analysis uses an intent-to-treat approach; updated information on haemoglobin concentrations was not available for study. It is possible that correction of anaemia after baseline occurred, which would lead to a bias towards a finding of no association. This is a potential limitation that is shared with virtually all other outcome studies of anaemia. While we cannot rule out this possibility, the recent evidence of rather low treatment rates of KTR even with severe anemia in several large transplant centres would not suggest
so [1–6]. When comparing the haemoglobin concentrations in those patients who were enrolled in both source populations, we found Hb to be stable over time (mean difference in Hb = −0.2 g/dl) and to correlate highly between the two measurements that were taken a mean 16 months apart (P = 0.74; P < 0.001). We had no information on cigarette smoking, lipid concentrations and blood pressure in these KTR. It is unclear whether absence of these factors confounds the associations found. The portfolio of immunosuppressive therapeutics has been expanded greatly over the past years, and some of the newer immunosuppressants have been implicated in being associated with a greater degree of anaemia [1–6,25,26]. While accounting for the exact immunosuppressive regimen did not change the results in this study, it is uncertain how immunosuppressive regimens that have become available more recently would influence similar studies. Lastly, while being the largest long-term follow-up available more recently would influence similar studies.

We conclude from this study that anaemia may not be substantially associated with all-cause mortality in KTR, which is in contrast to findings from other populations. The association between anaemia and kidney allograft loss may reflect our limited ability to control for underlying inflammatory processes or other unmeasured factors. Clear symptoms from anaemia may constitute an indication for rh-Epo treatment in KTR, and correction of anaemia may increase health-related quality of life in such patients [27]. It is unclear at this time whether correction of anaemia in the asymptomatic patient is an important clinical priority given its cost. Further study, especially evidence from randomized controlled trials specifically in KTR [28], is needed to guide clinicians in the treatment of anaemia in these patients.

Conflict of interest statement. None declared.

References


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