Impact of Erythropoiesis Stimulating Agents (ESA) Use on Renal Transplant Graft Survival

MEDCAC

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Anemia of CKD

- **Chronic kidney disease (CKD) is a continuum and includes patients on dialysis and those not yet on dialysis**
- **CKD is frequently complicated by anemia and potentially blood transfusion requirements.**

High PRA is Associated with Worse Outcomes

- **In patients with CKD, blood transfusions are associated with high panel reactive antibody (PRA) titers.**
- **High PRA can preclude or delay time to renal transplantation**
- **High PRA are associated with worsened graft survival.**

Epoetin Alfa Decreases Transfusion Needs

- **Epoetin alfa, an ESA, is FDA-approved to elevate hemoglobin (Hb) levels and decrease transfusion needs for patients with CKD.**
- **FDA-approved prescribing information recommends maintaining hemoglobin levels between 10 -12 g/dL**

CRDAC Does Not Recommend Changing the Current ESA Label

- **The majority vote of the October 2010 Cardiovascular and Renal Drug Advisory Committee (CRDAC) recommended that darbepoetin alfa continue to be indicated for treatment of anemia in CKD patients not on dialysis and the dose-schedule in the TREAT study control arm not be adopted for CKD patients.**

Anemia and Chronic Kidney Disease (CKD)

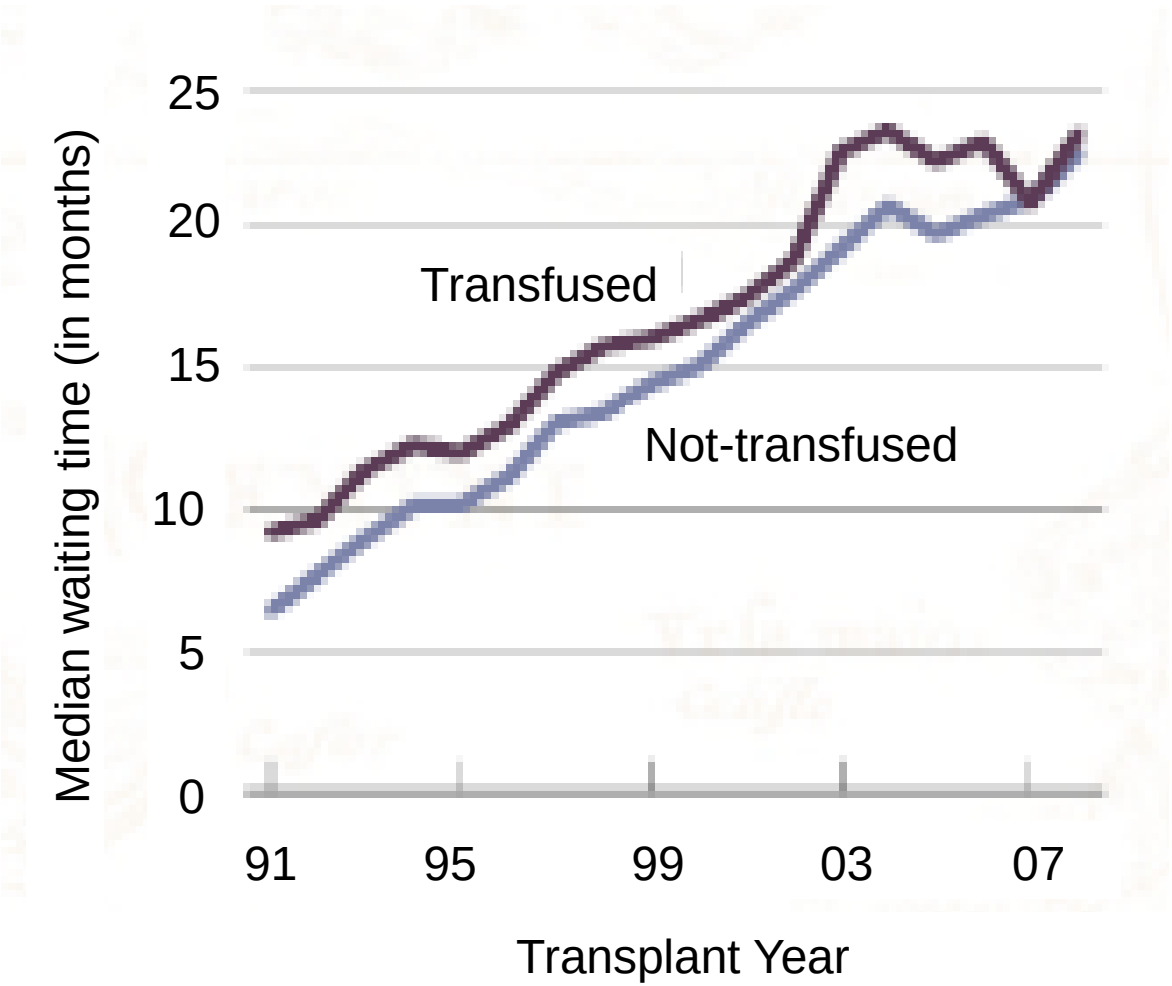
- CKD is a spectrum of disease that ranges from minor to severe impairment of kidney function[1]
- As kidney function declines, erythropoietin production declines, leading to progressive anemia
- Interventions may include:
  - Blood transfusions
  - Iron supplementation (when medically indicated)
  - Support with ESAs

[1]Mehrotra R, *Perit Dial Int*. 2007; 27:125-30.

Blood Transfusions in Patients with CKD

- 28% of transplant recipients receive at least one RBC transfusion within the first 3 years on the transplant list
- The median time to renal transplantation is longer for those CKD patients that received a pre-transplant RBC transfusion compared to those that did not

Transplant List Waiting Time

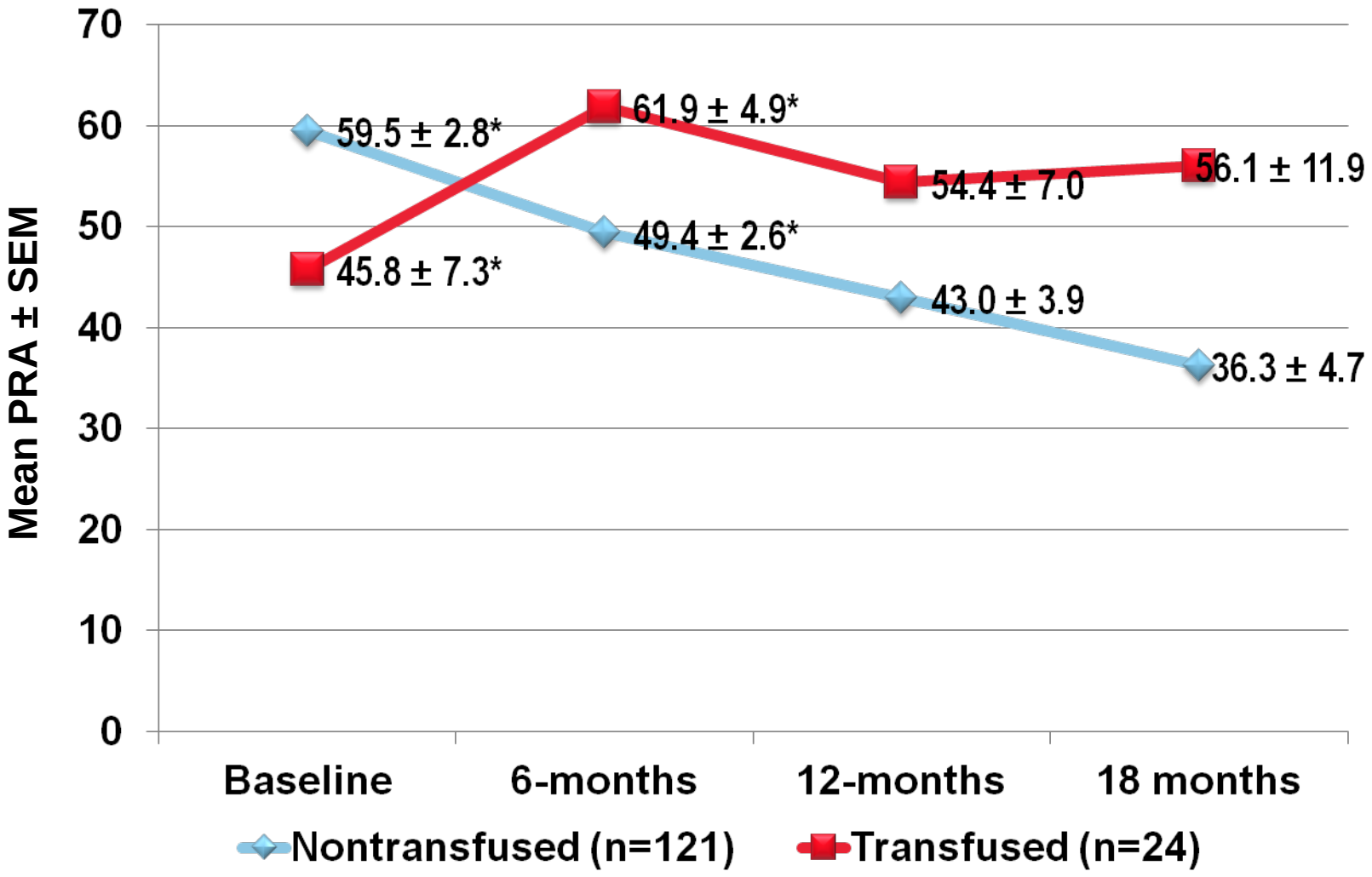


USRDS 2010

Panel Reactive Antibodies (PRA)

- RBC transfusion exposure during the pre-transplant period has been associated with a higher level of PRA
- PRA is associated with longer time on the wait list for renal transplantation, higher rates of hyper-acute rejection, accelerated acute rejection, antibody-mediated rejection, delayed graft function, and longer term complications

PRA Levels and Transfusions



** P=0.05*

Deierhoi et al., *Transplantation*.1992;53(2):363-368.

PRA Levels Affect Transplant List Wait Time

- Wait time for transplant candidates in 2005 was evaluated based on the median time to transplantation

	PRA 0%	PRA 1- 19%	PRA 20-79%	PRA ≥ 80%
Median time to transplant, years	2.5	2.9	4.3	Yet to be determined

- Longer wait times are a result of the greater difficulty of finding appropriate crossmatch for the transplant candidate

Lopez-Hoyos M, et al., *Hum Innunol.*2005;66:371-377.

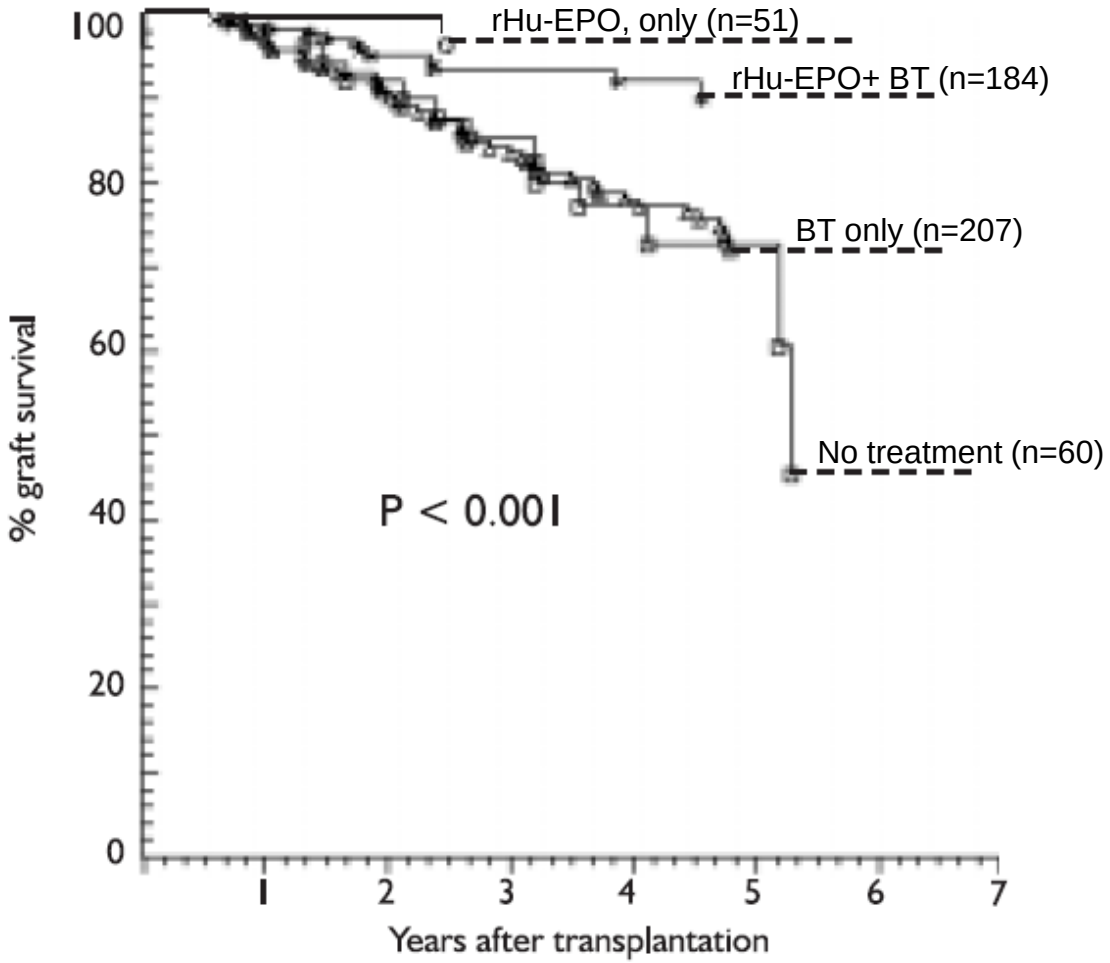
Blood Transfusions and Graft Loss

(N=93,026)

- Pre-transplant transfusions were associated with increased odds of PRA >10% at the time of transplantation
  - Men OR: 1.63 (1.52-1.74)
  - Women OR: 1.62 (1.58-1.73)
- PRA>10% at the time of transplant was associated with an increased risk of graft failure through 6-years post-transplant in patients transplanted 1999-2004
  - RR 1.18 (1.12-1.25)

Ibrahim et al. *Am J Kidney Dis*. 2009; 53(4):A43.

Pre-transplant Therapy with rHu-EPO Improves Long-term Graft Survival



Lietz K, et al. *Ann Transplantion*. 2003; 8(2):17-25.

Epoetin Alfa Indication

- Epoetin alfa is indicated for the treatment of anemia associated with CKD, including patients on dialysis and patients not on dialysis.
- Epoetin alfa is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. Patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.
- Epoetin alfa is not intended for patients who require immediate correction of severe anemia.
- Epoetin alfa may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

PROCRIT (epoetin alfa). Prescribing information. Centocor Ortho Biotech, Inc.

CRDAC Recommends No Change to the Current Label for ESAs Use in CKD

- Aranesp should continue to be indicated to treat anemia in CRF patients not on dialysis
- Current dosing schedule for Aranesp should not be changed to the placebo group regimen used in TREAT

	Vote	
	Yes	No
Should the indication for Aranesp for the treatment of anemia associated with CRF for patients not on dialysis be withdrawn?	1	15
If Aranesp continues to be marketed for the treatment of anemia in patients with CRF not on dialysis, should the control group regimen as used in TREAT be adopted as the dose-schedule for use in patients not on dialysis?	5	9
Should the control arm regimen as used in TREAT be adopted as the dose-schedule for use for the anemia associated with CRF in dialysis patients?	2	13
Should the use of Aranesp be avoided for all patients with CRF with a prior history of stroke?	4	10

www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee?ucm192863.htm.

Summary

- **CKD is a continuum of disease that is frequently complicated by anemia and potentially blood transfusion requirements.**
- **In patients with CKD, transfusion are associated with high panel reactive antibody (PRA) titers that can preclude or delay time to renal transplantation and are associated with worse graft survival.**
- **Epoetin alfa is FDA-approved to elevate hemoglobin levels and decrease transfusion needs for patients with CKD. The recommended target for treatment is a Hb of 10-12 g/dL.**
- **The majority vote of the October 2010 CRDAC recommended that darbepoetin alfa continue to be indicated for treatment of anemia in CKD patients not on dialysis and the dose-schedule in the TREAT study control arm not be adopted for CKD patients.**