Immunology/Transplantation and Nephrology PRNs’ Focus Session—Long-term Management of the Renal Transplant Recipient
Activity No. 0217-0000-11-076-L01-P (Knowledge-Based Activity)

Monday, October 17
1:30 p.m.–3:30 p.m.
Convention Center: Rooms 319 & 320

Moderators: Heather A. Nyman, Pharm.D., BCPS
Clinical Pharmacist, Dialysis, University of Utah Dialysis Program, Salt Lake City, Utah

and

Angela Q. Maldonado, Pharm.D., BCPS
Clinical Assistant Professor of Pharmacotherapy, Washington State University; Kidney Transplant Pharmacist, Providence Hospital, Spokane, Washington

Agenda

1:30 p.m.  Introduction and Welcome

1:40 p.m.  Mineral and Bone Disorder in Chronic Kidney Disease and Kidney Transplantation
Timothy M. Clifford, Pharm.D., BCPS
Clinical Pharmacist Specialist–Transplant/Critical Care; Assistant Adjunct Professor, Pharmacy and Surgery, University of Kentucky, Lexington, Kentucky

2:15 p.m.  Anemia Pre- and Post-renal Transplant—Shouldn’t the Allograft Be the Cure?
Joanna Q. Hudson, Pharm.D., FASN, BCPS
Associate Professor, The University of Tennessee, Departments of Clinical Pharmacy & Medicine (Nephrology), Memphis, Tennessee

2:50 p.m.  The Pharmacokinetics and Pharmacodynamics of Drug Dosing in the Renal Allograft Recipient
Ali Olyaei, Pharm.D.
Professor of Medicine, Director of Clinical Research, Division of Nephrology and Hypertension, Oregon State University/Oregon Health & Sciences University, Portland, Oregon

3:25 p.m.  Closing Remarks

Faculty Conflict of Interest Disclosures

Timothy M. Clifford: no conflicts to disclose.
Joanna Q. Hudson: speaker’s bureau for Amgen.
Ali Olyaei: no conflicts to disclose.
Learning Objectives

1. Discuss the pathophysiology of mineral and bone disorder (MBD) in the CKD patient.
2. Discuss the prevalence of MBD in the kidney transplant recipient.
3. Describe the methods of diagnosing MBD, goals of management and monitoring parameters.
4. Recommend non-pharmacological and pharmacological treatment of MBD.
5. Discuss the pathophysiology of anemia both pre- and post-renal transplant.
6. Describe the goals of therapy and pharmacological management of anemia.
7. Describe the conflicting data on target hemoglobin with the use of erythropoiesis stimulating agents.
8. Describe the various methods of estimating GFR in the renal allograft recipient.
9. Discuss the use of potentially nephrotoxic medications in the renal allograft recipient and how to minimize nephrotoxicity.
10. Discuss how the varying degree of renal insufficiency affects the pharmacokinetics and pharmacodynamics of the immunosuppressants.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Anemia Pre- and Post-Renal Transplant – Shouldn’t the Allograft Be the Cure?

Joanna Hudson, Pharm.D., BCPS, FASN
Associate Professor
Departments of Clinical Pharmacy & Medicine (Nephrology)
The University of Tennessee
Memphis, TN

Objectives
• Discuss the pathophysiology of anemia both pre- and post-renal transplant
• Describe the goals of therapy and pharmacological management of anemia
• Describe the conflicting data on target hemoglobin with the use of erythropoiesis stimulating agents

Erythropoiesis in CKD

Response to ↓ RBC Mass

Contributing Factors of Anemia Associated With CKD
• Erythropoietin deficiency & resistance
• Chronic blood loss
• Shortened RBC lifespan from 120 to ~60 days
• Iron losses (iron deficiency)
  – GI bleeding
  – Reduced intake & absorption
• Malnutrition
• Inflammatory conditions
• Hemodilution
• Secondary Hyperparathyroidism
• Other disease states (e.g. cancer, HIV)
Anemia Post Transplant

- At time of kidney transplantation almost all patients have anemia of CKD
- Post-transplantation anemia (PTA) is estimated to occur in 30-40% of patients
- Anemia usually resolves by 3-6 months, but some patients have late PTA defined as anemia ≥ 6 to 12 months after transplant
- Use of ESAs in kidney transplant recipients is relatively low

Mechanisms of PTA

- Decreased RBC Production
  - Drug induced (immunosuppressants, ACEIs/ARBs, antimicrobial agents)
  - Allograft dysfunction and rejection
  - Erythropoietin resistance (iron deficiency, infections, aplastic anemia)
- Loss of RBCs
  - Surgical blood loss
  - GI blood loss
  - Frequent phlebotomy

Mechanisms of PTA

- Increased RBC destruction
  - Immune-mediated hemolysis (immunosuppression, PTLD)
  - Microangiopathic hemolytic anemia (tacrolimus, cyclosporine, sirolimus)
  - Nonimmune hemolysis (G6PD deficiency – dapsone, trim/sulf, hemoglobinopathies)
- Other factors
  - Donor and recipient factors
  - Limitations of iron indices in transplant population
  - Elevated hepcidin levels
Immunosuppressive Medications and Anemia

- Antimetabolite medications (azathioprine, MMF, mycophenolic acid) → bone marrow suppression
- mTOR inhibitors (sirolimus, everolimus) → myelosuppression and other mechanisms
- Hemolytic anemia with sirolimus and the calcineurin inhibitors tacrolimus and cyclosporine

Role of Hepcidin in Iron Metabolism

- Hormone produced primarily in the liver
- Principal regulator of iron absorption and distribution into tissues
- ♦ hepcidin → blocks iron absorption
- ♣ hepcidin → increases iron absorption

Iron deficiency, Increased erythropoiesis

LIVER

Hepcidin

† Hepcidin

Increased iron stores

Inflammation

Prevalence of PTA

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Hb &gt; 12 g/dL</td>
<td>Hb &gt; 12 g/dL</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hb &gt; 11 - 12 g/dL</td>
<td>Hb &gt; 11 - 12 g/dL</td>
</tr>
<tr>
<td>Severe</td>
<td>Hb ≤ 11 g/dL</td>
<td>Hb ≤ 11 g/dL</td>
</tr>
</tbody>
</table>

ESA therapy was used in 5.2% of patients overall and in 18% of patients with severe anemia.

Association with GFR

Among pts with Hct < 30% 36% had iron studies 48% received iron 40% ESA
Consequences in Transplant?

- Anemia significantly associated with
  - mortality (hazard ratio 1.69; 95% CI 1.15 – 2.5)\(^1\)
  - graft failure (hazard ratio 2.47; 95% CI 1.47-4.10)\(^1\)
  - Left ventricular growth\(^2\)
- Anemia not related to all-cause mortality but associated with 25% risk of allograft loss (hazard ratio 1.25; 95% CI 1.02-1.59)\(^3\)


Consequences in Transplant?

- Not a clear consensus than anemia is associated with increased mortality and adverse CV events in transplant population
  - Anemia may not directly cause adverse outcomes in transplant population, but may be a marker for an underlying pathologic process

Goals in Transplant Patient

Balance goals while minimizing the risks of treatment.

Approach to Prevention and Treatment

- Perioperatively: Consider iron for patients with transferrin saturation < 20% and serum ferritin < 200 ng/mL
- Consider ESA therapy when benefit outweighs risk

K/DOQI Guidelines for Anemia Management in the Transplant Population

- Recommend that treatment guidelines for anemia in the general CKD population be followed in the transplant population
- ESAs Early Post-transplantation
  - Studies support that ESAs are effective in correcting anemia, although higher doses may be required compared to doses pre-transplant
- ESAs Late Post-transplantation
  - ESAs are effective and do not likely accelerate a decline in renal function
  - May contribute to hypertension

Guidelines for Anemia of CKD

What is known about ESAs in the transplant population?

- ESA therapy post-transplant shortens time to achieve higher hematocrit and improves QOL.¹ ²
- Observational studies in kidney transplant show evidence of increase mortality with Hb levels above 12.5 g/dL.³
- Medicare reimbursement polices affect therapy

Questions about ESAs in the transplant population?

- Can we apply data from ESA studies in CKD population?
- When do we start treatment and how aggressive should we be?
- What is the target Hb?

Concerns with ESAs and Target Hb in CKD...

Mean monthly hemoglobin & mean EPO dose per week

United States Renal Data System (USRDS) 2006 Annual Data Report

Safety Information on ESAs:
Supporting Studies

**WARNINGS: Increased Mortality and Serious Cardiovascular Events**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Sponsor</th>
<th>Published</th>
<th>Target Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basurto et al (Epoetin alfa)</td>
<td>Cardiac disease on hemodialysis</td>
<td>Amgen</td>
<td>1066</td>
<td>14 ± 1 vs 10 ± 1</td>
</tr>
<tr>
<td>CHOIR Trial (Epoetin alfa)</td>
<td>Anemia associated with CKD not on dialysis</td>
<td>Ortho Biotech/ J &amp; J</td>
<td>2006</td>
<td>13.2 vs 11.3</td>
</tr>
<tr>
<td>CREATE Trial (Epoetin beta)</td>
<td>Anemia associated with CKD not on dialysis</td>
<td>Hoffmann-La Roche</td>
<td>2006</td>
<td>13-15 g/dL vs 10.5-11.5 g/dL</td>
</tr>
</tbody>
</table>

**CHOIR Trial**

Primary endpoints: time to composite death, MI, stroke, death, CHF hospitalization

- 715 assigned to high-Hb group (13.3 g/dL)
- 717 assigned to low-Hb group (11.3 g/dL)

- 312 completed 36 months or withdrew at study termination without having primary event
- 125 had a primary event
- 278 withdrew before early termination of study
  - 131 required RRT
  - 147 withdrew for other reasons

- 349 completed 36 months or withdrew at study termination without having primary event
- 97 had a primary event
- 271 withdrew before early termination of study
  - 111 required RRT
  - 160 withdrew for other reasons


**CHOIR Study**


Primary Composite End Point

- N = 1432

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Hemoglobin Level (g/dL)</th>
</tr>
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<tbody>
<tr>
<td>High-hemoglobin group</td>
<td>13.6</td>
</tr>
<tr>
<td>Low-hemoglobin group</td>
<td>11.4</td>
</tr>
</tbody>
</table>

- 223 composite events (death, MI, hospitalization for CHF, stroke)
- High-Hb (13.5 g/dL): 125 events (18%)
- Low-Hb (11.3 g/dL): 97 events (14%)
- Hazard ratio (HR) = 1.34; 95% Confidence Interval (CI), 1.03 to 1.74 (P = 0.03)

**CREATE Study**

- 603 patients with CKD stage 3 or 4 randomly assigned to 1 of 2 groups:
  - Epoetin beta therapy targeted to Hb 13.0-15.0 g/dL
  - Epoetin beta therapy targeted to Hb 10.5-11.5 g/dL
- Primary endpoint was time to first cardiovascular event
- Secondary endpoints were LVMI, QOL, and progression of CKD

**Median Hemoglobin Levels in the Intention-to-Treat Population During the Study**


**Time to Primary End Point of First Cardiovascular Event**


**CREATE Study**

- There was no difference between the groups in the primary endpoint, LVMI, or progression of CKD
- QOL increased significantly in both groups, but was significantly better in the higher Hb group compared with the lower Hb group at yr 1


**Meta-Analysis of CKD Trials**

FDA Reaction to Safety Information on ESAs

- FDA issued warning in late 2006 regarding new risks associated with use of ESAs
- FDA changed labeling for ESA on March 9, 2007
- The use of ESAs may increase the risk for death and for serious cardiovascular events when dosed to achieve a target hemoglobin of >12 g/dL
- FDA recommends using the lowest dose of ESAs that will gradually raise the hemoglobin concentration to the lowest level sufficient to avoid the need for blood transfusion


Black Box Warning for ESAs in CKD

Renal failure: Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

K/DOQI - 2007 Update of Hb Target

Adequate Hb

| Lower limit of Hb (Recommendation) | • In dialysis and nondialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11-12 g/dL |
| Upper limit of Hb (Guideline) | • In dialysis and nondialysis CKD patients receiving ESA therapy, the Hb target should not be above 13 g/dL |

Strength of evidence = moderate


TREAT: Trial to Reduce Cardiovascular Events with Aranesp® (Darbepoetin alfa) Therapy

Hypothesis:
Treatment of anemia with darbepoetin reduces the risk of mortality and cardiovascular events and ESRD in patients with CKD and type 2 diabetes

Study Population:
- Hb < 11 g/dL
- GFR 20-60 mL/min
- Type 2 DM
- TSat ≥ 15%

Design – randomized (1:1), double blind, controlled

N = 2012 Darbepoetin Group (Target Hb 13 g/dL)
N = 4435
N = 2026 Control Group

TREAT End Points

Primary Endpoints – Time to:
- Composite outcome of death from any cause or a CV event defined as:
  - Nonfatal myocardial infection
  - Congestive heart failure
  - Stroke
  - Hospitalization for myocardial ischemia
- Composite of death or ESRD

Secondary Endpoints – Time to:
- Death
- Death from CV causes
- Rate of decline in eGFR
- Change in patient reported fatigue (FACT-fatigue)

TREAT

- TREAT failed to meet its primary objectives of demonstrating a reduction in all-cause mortality, CV morbidity, or ESRD and in time to all-cause mortality or ESRD.
- There was an almost two-fold increase in risk of stroke (5% in treatment arm vs. 2.6% in placebo arm)
- Among darbepoetin treated subjects with a past history of cancer, there were more deaths due to all causes and due to cancer compared with the control group

“FDA Urges Lower Doses of Anemia Drugs”

Reported that the FDA “said that three drugs that had been widely used to treat anemia in both kidney and cancer patients were so dangerous to the heart that doctors should consider avoiding the medicines altogether in some patients and using less of them in others.” The FDA “concluded that there were no risk-free doses of Epogen (epoetin alfa), Aranesp (darbepoetin alfa) and Procrit (epoetin alfa), and that doctors should use the medicines only in patients suffering from severe anemia.


Most Recent Black Box Warning for ESAs in CKD

<table>
<thead>
<tr>
<th>Chronic Kidney Disease:</th>
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<tbody>
<tr>
<td>In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.</td>
</tr>
<tr>
<td>No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.</td>
</tr>
<tr>
<td>Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions.</td>
</tr>
</tbody>
</table>

Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

Epogen® PI, Amgen Inc. – June 2011

Labeling of ESAs

For patients with CKD on dialysis:
- Initiate Epogen treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose

For patients with CKD not on dialysis:
- Consider initiating Epogen treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and;
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Epogen, and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions.

Epogen® PI, Amgen Inc. – June 2011

Questions

- Are negative outcomes associated with ESAs specifically or Hb level or both?
- What is the Hb level at which QOL is maximixed, yet risk is minimized?
- Is iron a contributing factor or would increased use be supported to achieve target Hb without increased use of ESAs?
- What to do with conflicting FDA warnings and K/DOQI anemia guidelines?

Considerations in the Transplant Population

- Consider the risk of CV events and stroke in transplant recipients before initiating an ESA
- If blood transfusions are likely to be needed given the decline in Hb consider potential benefit of ESAs at low Hb (< 10 g/dL)?
- Until further guidance is available in the transplant population consider recommendations for ESA use in CKD patients not on dialysis
Summary

• Anemia of CKD is prevalent in patients post-kidney transplant and a problem many practitioners will be faced with given the increase in the population with ESRD.

• Iron supplementation and ESAs are essential for treatment of anemia of CKD; however, practitioners need to be cognizant of the limitations in using these agents.

• Recent evidence of mortality risk associated with higher Hb in select populations has raised many questions about the current strategies for anemia management.

• Whether the same risks of ESA use observed in the CKD population apply to kidney transplant patients has not been determined; however, there is enough information on ESAs to justify caution when making treatment decisions for individuals with anemia post transplant.