Comparison of induction strategies in renal transplantation: Who gets what?

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Learning Objectives
- Understand the immune targets important in transplant immunology
- Identify common immunosuppression agents used in kidney transplantation
- Recognize important donor and recipient factors for rejection
- Evaluate available induction agents and their evidence in kidney transplant
Comparison of induction strategies in renal transplantation

I. Kidney disease in the United States\textsuperscript{1, 2}
   A. Estimated 13.6\% of adults have some level of chronic kidney disease (CKD) making it more common than diabetes mellitus (12.3\%)
   B. End Stage Renal Disease (ESRD) as of 2013
      1. Incidence rate of 363 new cases per million/year
      2. Prevalence rate of 2034 cases per million/year
      3. Deaths from ESRD rose to 90,119 patients in 2012
      4. Medicare expenditures up to $30.9 billion (7.1\% of claims)
   C. Most common causes of ESRD
      1. Diabetes (nephropathy)
      2. Hypertension
      3. Glomerulonephritis
      4. Other diseases of genetic etiology

II. Options for patients with ESRD\textsuperscript{3, 4}
   A. Dialysis
      1. Roughly 400,000 patients treated with dialysis each year
      2. Death rate for dialysis patients now 20\% per year
      3. Hemodialysis expenditures > $80,000/patient in 2009
   B. Kidney transplantation
      1. Optimal treatment modality for ESRD
         a. Longer survival & better quality of life for most vs. dialysis
         b. Five-year survival: transplant (85.5\%) vs. dialysis (35.8\%)
      2. Surgical intervention
         a. One-year cost of dialysis nearly triple that of transplant
         b. Re-hospitalization rate higher in first year, then lower in longitudinally consuming fewer healthcare resources

\begin{center}
\includegraphics[width=\textwidth]{patient_survival_rates.png}
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www.niddk.nih.gov/health-information/health-statistics/documents
Comparison of induction strategies in renal transplantation

3. Allograft options
   a. Deceased donation (DD) – from an immunologically compatible cadaver after brain or cardiac death
      i. Consideration for cause of death, ischemia time, and donor health
      ii. One-year patient (95%) and graft survival (92%) inferior to living donation
      iii. Kidney Donor Profile Index (KDPI) is a numerical measure to express donor kidney quality
           • KDPI 70% has higher expected risk of graft failure than 70% of kidneys recovered
           • Allows clinician to allocate a kidney to a recipient of similar survival expectations
           • Improvement upon and replaced less inclusive expanded criteria donation (ECD)
   b. Living donation (LD) – from an immunologically compatible friend, family member, or altruistic donor
      i. Highly coordinated effort (minimal ischemia time)
      ii. One-year patient (98%) and graft survival (97%)

4. Prospective recipients on the national transplant waiting list greatly outnumber donor supply
   a. Over 100,000 patients awaiting a kidney (January 2016)
   b. Only 17,104 kidney transplants between in 2014

5. 1-year graft survival key in outcomes

III. Transplant immunology
   A. Target cells for transplantation are of lymphocyte lineage
   B. Lymphocytes mature into T- and B-cells
      1. T-cells responsible for cellular rejection
      2. B-cells responsible for antibody-mediated rejection

http://www.textbookosacteriology.net/cellsindefenses75.jpg
C. Cell- vs. antibody-mediated rejection

1. Hyperacute: occurs within minutes to hours
   a. Pre-formed donor specific antibodies (DSA) react with donor antigen to activate complement
   b. Mostly prevented by pre-transplant tissue/blood matching

2. Acute: occurs within weeks to months
   a. Acute cellular rejection (ACR)
      i. Infiltration of graft by lymphocytes and other inflammatory cells
      ii. Prevention is primary goal of maintenance immunosuppression
      iii. Mild ACR treated with steroids, whereas more severe ACR requires antibody treatment
   b. Antibody-mediated rejection (AMR)
      i. Caused by de-novo DSA leading to complement activation in the graft
      ii. Differs from ACR, but often mixed rejection

3. Chronic AMR: occurs over months to years
   a. Slow, indolent process leading to graft function decline
   b. Often due to sub-optimal immunosuppression adherence

D. Immune discrimination

1. Human leukocyte antigen (HLA) is a cell surface marker that distinguishes self from non-self
   a. Class 1 (HLA-A, -B, and -C)
      i. Expressed on all nucleated cells
      ii. Presents antigenic intracellular peptides to cytotoxic CD8\(^+\) T-cells
   b. Class 2 (HLA-DR, -DP, and -DQ)
      i. Expressed on antigen presenting cells (APC) which are macrophages, dendritic cells, B-cells
      ii. Presents processed extracellular peptides to helper CD4\(^+\) T\(_h\)-cells
   c. HLA-A, -B, and −DR matching historically important for rejection risk in kidney transplantation

2. Innate immune system
   a. Fast (minutes to hours), non-specific onset, short duration
   b. Primitive and indiscriminate immune response
   c. Very little amplification; no memory of foreign contacts

3. Adaptive (acquired) immune system
   a. Slow (days to weeks), highly specific response, long duration (months to years)
   b. Highly orchestrated activation of immune response
   c. Amplification and cell-talk allows antigen memory
Comparison of induction strategies in renal transplantation

4. CD4⁺ Th-cell proliferation orchestrates the rejection response
   a. Focus of maintenance immunosuppression
   b. 3 signal pathway activated by antigen presentation
      i. Signal 1
         • Antigen presented to CD4⁺ Th-cell
         • Binding produces IL-2 chemokine
      ii. Signal 2
         • APC binds co-stimulatory CD28 receptor
         • CD4⁺ Th-cell activation threshold lowered
      iii. Signal 3
         • IL-2 binds CD25 receptor
         • Stimulates mTOR → CD4⁺ Th-cell proliferation

E. Pre-transplant HLA antibodies
   1. Panel reactive antibody (PRA): expressed as a percentage and reflects recipients’ ability to produce antibody to HLA in general population, better known as “sensitization”
   2. Sensitization increases with prior exposure to non-self HLA:
      a. Previous transplant, nephrectomy
      b. Blood transfusions
      c. Pregnancy
   3. Crossmatch (XM): determine compatibility with a specific donor prior to transplant
      a. Positive XM indicates presence of preformed DSA and transplant is typically not suitable
      b. Different XM tests available to clarify questionable mismatches and predict immunologic consequences

IV. Donor and recipient risk factors for acute rejection\textsuperscript{14-16}
   A. Number of HLA mismatches
   B. Younger recipient age and older donor age
   C. African-American ethnicity
   D. PRA > 0%
   E. Presence of DSA
   F. ABO blood group incompatibility
   G. Delayed graft function (DGF)
      1. Influenced by organ quality and cold ischemia time
      2. Defined as requiring dialysis during first post-op week
   H. Cold ischemia time (CIT)
      1. Time when donor organ is on ice during transportation
      2. Significantly greater risk of DGF when greater than 24 hours
V. Immunosuppression (IS) 2.17-20

A. Goal is to prevent rejection and prolong graft survival while minimizing opportunistic infections, malignancies, and side effects

B. Components of IS therapy
   1. Maintenance – chronic IS used to minimize rejection
   2. Induction – potent IS used perioperatively
   3. Rescue – treatment of rejection

C. Evolution of IS
   1. First kidney transplant failed due to lack of IS
   2. Introduction of first calcineurin inhibitor, cyclosporine dramatically increased graft survival
   3. ACR rates now approximately 10% in the 1st year

D. Maintenance – chronic IS used to minimize rejection
   1. Typically consists of 2-3 classes of medications with different immune targets used together to minimize doses of each and, thus, reduce side effects
   2. Recent national data suggests that most transplant centers use a 3 drug regimen of tacrolimus (96.5%), mycophenolate mofetil (93%), and prednisone (65.6%) as of 2013
   3. Maintenance IS therapy:
      a. Calcineurin inhibitors (CNIs)
         i. Mechanism – inhibits CD4+ T_h-cells’ ability to produce IL-2 for activation of T and B lymphocytes
         ii. Tacrolimus (TAC)
            • ~0.1 mg/kg/day dosed every 12 hrs
            • Trough levels: 5 – 12 ng/mL with higher goal levels early and tapered later
            • Side effects: nephrotoxicity, neurotoxicity, and metabolic side effects
         iii. Cyclosporine (CyA) – 2nd line agent due to increased rejection
      b. Cell cycle inhibitors (antiproliferatives)
Comparison of induction strategies in renal transplantation

i. **Mechanism** – inhibit S phase of T- and B-cell proliferation

ii. **Mycophenolic acid**
   - 1000 mg BID (mycophenolate mofetil, MMF)
   - Side effects: GI side effects and bone marrow suppression (pancytopenias)

iii. **Azathioprine** – 2nd line agent due to increased rejection and hematological side effects

c. **Corticosteroids (CS)**
   i. **Mechanism** – interfere with important signals for the recruitment of immune cells to the rejection process
   ii. **Prednisone** – only maintenance oral steroid
      - High doses of IV methylprednisolone doses used perioperatively, tapered off or to maintenance prednisone dose
      - Limited by metabolic effects, mainly hyperglycemia and hypertension

d. **Opportunistic infections (OI) common and require prophylaxis (ppx) in kidney transplant recipients:**
   - UTI, PCP, *Nocardia spp.*: SMZ/TMP
   - CMV: valganciclovir +/- adjuncts
   - BK virus: IS reduction +/- adjuncts
   - *Candida spp.*: nystatin,azole antifungals

E. **Induction** – potent antibodies used intra- and peri-operatively to deplete or modulate to T-cell response at the time of antigen presentation
   1. Provides background protection while maintenance immunosuppression is titrated to therapeutic levels
   2. **Classification of induction agents**
      a. **Antibody target**
         i. Monoclonal: basiliximab, alemtuzumab
         ii. Polyclonal: antithymocyte globulin
      b. **Depletion activity**
         i. Lymphocyte depleting: antithymocyte globulin, alemtuzumab
         ii. Non-lymphocyte depleting: basiliximab
VI. IL-2 receptor antagonist (IL-2RA) $^{17, 21, 24}$
   A. Mechanism
      1. Monoclonal, non-lymphocyte depleting agent
      2. IL-2 receptor antagonist (IL2-RA) found on activated T- and B-cells to stimulate lymphocyte proliferation
   B. Agent
      1. Basiliximab (Simulect®)
      2. Daclizumab (Zenapax®): withdrawn from market in 2009
   C. Dosing – basiliximab 20 mg IV intraoperatively and post-op day (POD) 4
   D. Side effects – well tolerated
   E. Cost – $6489.14 for induction (2 doses)

VII. Antithymocyte globulin $^{17, 22, 24}$
   A. Mechanism
      1. Polyclonal, lymphocyte depleting agent
      2. Target HLA and many immune cell receptors to cause cellular inactivation, lysis, and depletion
   B. Agents
      1. rATG (Thymoglobulin®) – rabbit
      2. ATG (ATGAM®) – horse; not used due to increased rejection
   C. Dose
      1. ~ 6 mg/kg divided into doses (1st dose intraoperatively)
      2. Requires premedication with APAP, diphenhydramine, steroids
   D. Side effects – thrombocytopenia, leukopenia, infusion reactions
   E. Cost – $12,757.60 for a 70-kg recipient (6 mg/kg)

VIII. Alemtuzumab, ALEM (Campath-1H®) $^{17, 23, 24}$
   A. Mechanism
      1. Monoclonal antibody, lymphocyte depleting agent
      2. Targets CD52 receptor and directs destruction of T- and B-cells
   B. Dose
      1. 30 mg IV intra-operatively x 1 dose
      2. Requires premedication with APAP, diphenhydramine, steroids
   C. Side effects – cytopenias, infusion reactions
   D. Cost – currently no charge through Campath® Distribution Program from manufacturer for the indication of transplant induction
Comparison of induction strategies in renal transplantation

What is the optimal induction agent in kidney transplant recipients? Or more appropriately . . . Who gets what?!

IX. Early studies comparing induction strategies
A. Basiliximab vs. placebo (Lawen 2003)\textsuperscript{25}
   1. Randomized, double blind, multicenter study
   2. Low-moderate risk receiving DD or HLA non-identical kidneys
   3. Induction: basiliximab 20 mg x 2 (n = 59) vs. placebo (n = 54)
   4. IS: CyA, MMF, prednisone
   5. OI ppx: SMZ/TMP; ganciclovir, acyclovir, or both if high CMV risk
   6. Results at 6 months
      a. First biopsy-proven rejection (BPAR): basiliximab (15.3%) vs. placebo (26.6%), \( p = \text{NS} \)
      b. Acute rejection (AR) treated with antibody: basiliximab (5.1%) vs. placebo (15.6%)
      c. Basiliximab significantly improved renal function in the first two weeks after transplant
      d. No difference between graft (GS) and patient (PS) survival at 12 months
      e. Adverse event profiles were similar
   7. Conclusion: basiliximab induction shows strong trend toward reduction in AR in kidney transplant recipients on triple IS; greatly decreased AR rates compared to basiliximab trials with recipients maintained on CyA and prednisone alone
B. Basiliximab vs. rATG (Brennan 2006, 2008)\textsuperscript{26,27}
   1. Prospective, randomized, international study
   2. High-risk for AR or DGF receiving DD kidney
   3. Induction: basiliximab 20 mg x 2 (n = 137) vs. rATG 1.5 mg/kg/day x 5 (n = 141)
   4. IS: CyA, MMF, prednisone
   5. OI ppx: IV/PO ganciclovir x 3 months if moderate-high risk for CMV, and anti-fungal & anti-bacterial per center protocol
   6. Results at 12 months
      a. BPAR: basiliximab (25.5%) vs. rATG (15.6%), \( p = 0.02 \)
      b. AR treated with antibody: basiliximab (8.0%) vs. rATG (1.4%), \( p = 0.005 \)
      c. Greater incidence of infection (85.8% vs. 75.2%, \( p=0.03 \)), but less CMV disease (7.8% vs. 17.5%, \( p=0.02 \)) with rATG
      d. More leukopenia (33.3% vs. 14.6%, \( p<0.001 \)), and higher trend of cancer (3.5% vs. 0.7%, \( p=\text{NS} \)) with rATG
      e. DGF, slowed graft function, GS, and PS were similar
7. Results at 5 years
   a. Less BPAR (15% vs. 27%, \( p=0.03 \)) and AR treated with antibody (3% vs. 12%, \( p=0.05 \)) with rATG
   b. rATG group had fewer cases of treated CMV (7% vs. 17%, \( p=0.04 \))
   c. No difference in cancer, graft or patient survival
8. Conclusion: while rATG did not reduce DGF in high risk recipients compared to basiliximab, rATG did reduce the incidence and severity of AR with lasting results

C. Basiliximab vs. alemtuzumab (Kaufman 2005)\(^{28}\)
   1. Single-center, non-randomized, retrospective, sequential study
   2. Varied risk recipients receiving DD or LD kidney where 37% of basiliximab vs. 25% of alemtuzumab received DD kidneys
   3. Induction: basiliximab 20 mg x 1 (n=155) vs. alemtuzumab 30 mg x 1 (n=123)
   4. IS: TAC, MMF + 3-day course of CS (no maintenance CS)
      a. 2.5-3 g MMF/day in basiliximab group
      b. 1.5-2 g MMF/day in alemtuzumab group
   5. OI ppx: SMZ/TMP, nystatin/clotrimazole, and (val)ganciclovir x 3 months if moderate-high risk CMV
   6. Results at minimum of 30 months
      a. Fewer episodes of AR with alemtuzumab in the first 3 months (4.1% vs. 11.6%), but equivalent at 12 months (14.9% vs. 13.5%, \( p = NS \))
      b. Median day to AR greater with alemtuzumab (153 vs. 10)
      c. Recipients in the alemtuzumab received significantly less TAC and MMF exposure at all points
      d. Infection and cancer rates were similar
      e. No difference in graft and patient survival at 1 and 3 years
7. Conclusion: current recommended dose of alemtuzumab induction shows similar efficacy as basiliximab in a prednisone-free maintenance protocol, although with increased rates of delayed AR episodes

X. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. \textit{Am J Transplant}. 2009. Chapter 1: Induction Therapy.\(^{14}\)
   A. Starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation (1A)
   B. Including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in recipients (1A)
      1. IL2-RA be the first-line induction (1B)
      2. Lymphocyte-depleting agent, rather than an IL2-RA, for high-immunologic risk recipients (2B)
   C. Base most recommendations on data from systematic reviews and meta-analyses in the older maintenance immunosuppression era
XI. Studies in the modern era of immunosuppression

A. Alemtuzumab vs. basiliximab and rATG (Hanaway 2011)\textsuperscript{29}

1. Prospective, randomized, multicenter, risk-stratified study
2. High-risk (repeat transplant, PRA > 20%, or black race) and low-risk receiving DD or LD (~60%) kidney; no ECD or DCD kidneys
3. Induction:
   a. Alemtuzumab 30 mg x 1 (n=164 low risk, n=70 high risk),
   b. Basiliximab 20 mg x 2 (n=171 low risk)
   c. rATG 1.5 mg/kg x 4 (n=69 high risk)
4. IS: TAC, MMF + 5 day course of CS (no maintenance CS)
5. OI ppx: per center protocol
6. Results at 36 months
   a. Low risk
      i. BPAR less with alemtuzumab at 36 months (10% vs. 22%, \textit{p}=0.003)
         • Similar rates of severe rejection and rejection requiring antibody
         • Late rejection >12 months trended higher with alemtuzumab (8% vs. 3%, \textit{p}=NS)
      ii. Serious infections higher with alemtuzumab (35% vs. 22%, \textit{p}=0.02) and mean lymphocyte count was lower at all time points
      iii. Graft and patient survival similar
   b. High risk
      i. Similar BPAR at 36 months between alemtuzumab (18%) and rATG (15%)
         • Similar rates of severe rejection and rejection requiring antibody
         • Late rejection >12 months trended higher with alemtuzumab (10% vs. 2%, \textit{p}=NS)
      ii. Serious infections and mean lymphocyte count were similar
      iii. Graft and patient survival similar
   c. Post-hoc analyses of biopsies: complement (C4d) staining, a marker for AMR, positive in 4% in the alemtuzumab vs. 1% in the combined basiliximab and rATG groups
7. Conclusion: alemtuzumab initially has less rejection than basiliximab in low risk recipients and equivalent rejection to rATG, although late-onset rejection may be concerning
Comparison of induction strategies in renal transplantation

B. Multivariate database analysis of DD recipients (Sureshkumar 2012) 30

1. Comparators: rATG (n=5348), alemtuzumab (n=2428), and IL-2RA (n=1396)
   a. Recipients were discharged on a CNI (primarily TAC) and MMF, but were not maintained on CS; received DD kidney
   b. Substantial demographic differences between groups, adjusted analysis based on covariates known to adversely impact graft outcome

2. Results
   a. Low risk
      i. Similar adjusted GS for alemtuzumab and IL-2RA vs. rATG
      ii. Alemtuzumab had similar adjusted PS, but IL-2RA had was lower (HR 1.16, 1.02-1.31) vs. rATG
      iii. Alemtuzumab had increased adjusted graft failure vs. rATG when PRA >20%, ECD, and CIT >24 hours
   b. High risk
      i. Lower adjusted graft survival for alemtuzumab (HR 1.18, 1.06-1.31) and IL-2RA (HR 1.06, 1.002-1.12)
      ii. Alemtuzumab had similar adjusted PS, but IL-2RA had was lower (HR 1.08, 1.004-1.17) vs. rATG
      iii. Alemtuzumab had inferior adjusted PS vs. rATG when ECD or CIT >24 hours

3. Conclusion: rATG seems to be associated with superior outcomes among DD kidney recipients maintained on CNI/MMF

C. rATG vs. alemtuzumab vs. IL-2RA, daclizumab (Ciancio 2014) 31

1. Prospective, randomized, single center study
2. Moderate-high risk recipients receiving DD or LD kidney; majority African-American and Hispanic
3. Induction: rATG 1 mg/kg x 7 (n=43), alemtuzumab 0.3 mg/kg x 2 (n=43), daclizumab 1 mg/kg x 5 (n=42)
4. IS:
   a. TAC, MMF, +/- CS
   b. Alemtuzumab group: lower TAC target, MMF 500 mg BID, and 7 day course of CS (no maintenance CS)
5. OI ppx: not described
6. Results (median follow up to 95 months)
   a. BPAR similar among the 3 groups (19% vs. 33% vs. 29%)
   b. Biopsy proven chronic allograft injury (CAI) higher with alemtuzumab (44%) vs. rATG (21%) + daclizumab (17%), p=0.0008 **Higher grade of CAI
   c. Death-censored graft failure higher with alemtuzumab (30%) vs. rATG (12%) + daclizumab (12%), p=0.009
      **Consistent between DD/LD and compliance
Comparison of induction strategies in renal transplantation

d. More recipients in the alemtuzumab (33%) had MMF withheld or discontinued MMF at 1 month vs. rATG (7%) + daclizumab (2%), p=0.00002 **WBC significantly lower in alemtuzumab group

e. 40% of alemtuzumab recipients required CS reinstitution

f. Similar rate of infection, new onset diabetes, and PS

7. Conclusion: long term results indicate inferior results with alemtuzumab induction with regard to CAI and graft failure in recipients maintained on reduced dose TAC and MMF

D. Alemtuzumab vs. rATG (Saull 2015)

1. Retrospective, single center study

2. Recipients: low risk (first transplant, PRA <20%); received DD or LD kidney
   a. More ECD in alemtuzumab group (likely due to exclusion of patients who received extended rATG due to DGF)
   b. Protocol biopsy at 1, 4, and 12 months

3. Induction: alemtuzumab 30 mg x 1 (n=100) vs. rATG 1.5 mg/kg x 4 (n=100)

4. IS: TAC, MMF + 5 day course of CS (no maintenance CS)

5. OI ppx: SMZ/TMP, nystatin/clotrimazole, and valganciclovir x 3 months if moderate and x 6 months in high risk CMV

6. Results at 12 months
   a. BPAR similar between alemtuzumab (34%) vs. rATG (23%)
   b. More severe grades of BPAR with alemtuzumab (p=0.047)
      i. Independently associated (OR 3.7, 1.2-10.5) regardless of ECD and DGF
      ii. Alemtuzumab only significant predictor for BPAR
   c. Median day to AR greater with alemtuzumab (182 vs. 30)
   d. Recurrent rejection more common with alemtuzumab (41% vs. 17%, p=0.05)
   e. More recipients in the alemtuzumab group with an MMF dose <1500 mg/day at first AR (84% vs. 16%) due to higher rates of BK virus, CMV disease, and leukopenia
   f. Similar rates of AMR: alemtuzumab (2%) and rATG (0%)
   g. Graft loss at 3 years: alemtuzumab (10) vs. rATG (5)

7. Conclusion: although rates of AR were comparable, more severe and delayed rejections were observed with alemtuzumab, potentially due to high rates of viral infection and leukopenia, with subsequent reduction in maintenance IS
XII. Cost comparison of induction and rejection\textsuperscript{24}

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<th>rATG</th>
<th>Alemtuzumab</th>
<th>Basiliximab</th>
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<tbody>
<tr>
<td>Induction Cost</td>
<td>$12,757.60 (up to 22,325.80)</td>
<td>Free</td>
<td>$6,489.14</td>
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<tr>
<td>Cost of Rejection</td>
<td>Incremental marginal costs per year post transplant in standard criteria donor recipients</td>
<td>With antibody therapy</td>
<td>With non-antibody therapy</td>
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<tr>
<td>1-year</td>
<td>$22,407</td>
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<td>2-years</td>
<td>$18,603</td>
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<td>3-years</td>
<td>$13,909</td>
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<tr>
<td>Cost of rATG for rejection</td>
<td>$22,325.80 to $44,651.60</td>
<td>Plus cost of IV methylprednisolone</td>
<td>Cost of IV methylprednisolone</td>
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<td>Totals</td>
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XIII. Conclusion

A. ALEM not recommended for inclusion into kidney transplant induction protocol
   1. May be a role in certain patients, although currently not clear
   2. Potential for future studies to optimize maintenance IS to be used with alemtuzumab

B. Induction agent selected based on risk stratification
   1. High-risk: rATG
   2. Low-risk: basiliximab

- High-risk
  - High PRA (>20%)
  - Re-transplant
  - Black race
  - Others at discretion (prolonged CIT, high risk for DGF, sub-optimal organ quality)

- Low-risk
  - Low PRA (<20%)
  - Infection or malignancy concern
XIV. References


21. Simulect® package insert

22. Thymoglobulin® package insert

23. Campath® package insert


