New Immunosuppression Horizons in Kidney Transplantation

Mumbai, India, February 9, 2014
New Immunosuppression Horizons

• “Golden Era” of RCTs
• KDIGO Guideline 2009
• Current Clinical Practice
• Recent Randomized Trials
• New Drug Development
Joseph Murray used total body radiation in 14 transplants — all died.

Murray & Calne used azathioprine in 6 transplants — all died.

Murray & Calne used azathioprine & 6-mercaptopurine used in 2 transplants — both died.

Murray & Calne treated rejection with steroids — Melvin Doucette went home!
Beginning the Era of RCTs

Equine ATG RCT (N=50)
Arch Surg 1976; 111:680

Canadian CsA RCT (N=209)
N Eng J Med 1983; 309:809

European CsA RCT (N=232)
Lancet 1983; 2:986

Kidney Disease: Improving Global Outcomes
New Immunosuppression Horizons

- “Golden Era” of RCTs
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Kidney Disease: Improving Global Outcomes

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

• Systematic reviews by the ERT: 1985 through January 2007
• Evidence updated through: November 2008
• GRADE system used

  Strength of Recommendations: 1 or 2

  Strength of Evidence: A, B, C, D

  “Not Graded” recommendations
Question 1

A 55 year old women with ESRD from diabetes has a living donor for her 1st kidney transplant. PRA 0%; no DSA. You would use the following induction:

A. No antibody induction
B. IL-2 receptor antagonist
C. Rabbit ATG
D. Alemtuzumab
E. Other
Question 2

A 55 year old women with ESRD from diabetes has a living donor for her 2nd kidney transplant. PRA 50%; no DSA. You would use the following induction:

A. No antibody induction
B. IL-2 receptor antagonist
C. Rabbit ATG
D. Alemtuzumab
E. Other
1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (1B)

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)
Maintenance Immunosuppression

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B)

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)
Maintenance Immunosuppression

3.2: We suggest that CNIs be continued rather than withdrawn. (2B)

3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C)
Treatment of Acute Cellular Rejection

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. \(1D\)

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. \(2D\)

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. \(2C\)
Treatment of AMR

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):

- plasma exchange;
- intravenous immunoglobulin;
- anti-CD20 antibody;
- lymphocyte-depleting antibody.
Treatment of Chronic Allograft Injury

7.2: For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C)

7.2.1: For patients with CAI, eGFR > 40 mL/min/1.73 m², and urine total protein excretion < 500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTORi. (2D)
New Immunosuppression Horizons

- “Golden Era” of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- Recent Randomized Trials
- New Drug Development
Induction Therapy

![Graph showing the comparison of different induction therapies over years]

- IL2-RA
- T-cell depleting
- None

Percent vs Year

OPTN / SRTR Annual Data Report  *Am J Transplant* Jan 2014
Maintenance CNI Use

- Tacrolimus
- Cyclosporine

Year

Percent

0 20 40 60 80 100

98 02 06 10
Maintenance Antimetabolite Use

![Graph showing maintenance antimetabolite use][1]

- **Percent**
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

- **Year**
  - 98
  - 02
  - 06
  - 10

- **Mycophenolate**
- **Azathioprine**

[1]: #![](image)
Maintenance mTOR Inhibitor Use

Percent

Year

At transplant
1 year post-tx

0 20 40 60 80 100

98 02 06 10
New Immunosuppression Horizons

- “Golden Era” of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- **Recent Randomized Trials**
- New Drug Development
Alemtuzumab: Anti-CD52 T-Cell & B-Cell–Depleting Monoclonal Antibody

Low Risk

(N=164) Alemtuzumab

(N=171) Basiliximab

Proportion Free from BPAR

Days since Transplantation

Kidney Disease: Improving Global Outcomes
Alemtuzumab: Anti-CD52 T-Cell & B-Cell–Depleting Monoclonal Antibody

*High-risk: repeat transplant, a peak or current value PRA > 20%, or black race.
Acute Rejection in BENEFIT & BENEFIT-EXT

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI (N=219)</th>
<th>Belatacept LI (N=226)</th>
<th>Cyclosporine A (N=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Rejection</td>
<td>49 (22%)</td>
<td>39 (17%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Banff grade IIA</td>
<td>17 (8%)</td>
<td>16 (7%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Banff grade IIB</td>
<td>20 (9%)</td>
<td>10 (4%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI (N=184)</th>
<th>Belatacept LI (N=175)</th>
<th>Cyclosporine A (N=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Rejection</td>
<td>33 (18%)</td>
<td>31 (18%)</td>
<td>26 (14%)</td>
</tr>
<tr>
<td>Banff grade IIA</td>
<td>10 (5%)</td>
<td>17 (10%)</td>
<td>17 (9%)</td>
</tr>
<tr>
<td>Banff grade IIB</td>
<td>16 (9%)</td>
<td>8 (5%)</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

Estimated GFR in BENEFIT-EXT

![Graph showing estimated GFR over time for different treatments.]

- **Bela MI**: 182, 177, 161, 153, 165, 145, 143, 140, 152, 129, 136, 139, 152
- **Bela LI**: 173, 168, 152, 149, 157, 140, 142, 144, 158, 139, 140, 132, 154
- **CsA**: 184, 172, 153, 147, 159, 139, 140, 137, 154, 126, 132, 133, 143

Safety Results in BENEFIT & BENEFIT-EXT

<table>
<thead>
<tr>
<th>Complication</th>
<th>Belatacept MI (N=403)</th>
<th>Belatacept LI (N=401)</th>
<th>Cyclosporine A (N=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTLD</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>
Late Switch from CNI to Belatacept

- Randomized, open-label trial:
  - Stable 6-36 months post-transplant
  - Group 1 (N=89): continue CNI
  - Group 2 (N=84): change to belatacept

<table>
<thead>
<tr>
<th>Complication</th>
<th>Belatacept (N=84)</th>
<th>Continue CNI (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>6 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Banff grade IIA</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Banff grade IIB</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Question 3

A 40 year old 1 year after a deceased donor kidney transplant is on tacrolimus, mycophenolate and prednisone 2.5 mg daily. You would consider switching tacrolimus to an mTOR inhibitor for decreasing eGFR from 60 to 50 mL/min/1.73m² with Banff Grade 1-2 interstitial fibrosis.

A. Yes
B. No
C. Unsure
Effect of Rapamycin Conversion at 1 Month on Interstitial Fibrosis at 1 and 2 Years

![Graph showing the percent with IFTA ≥ 2 at 1 month, 1 year, and 2 years for TAC and SRL.]

- **1 Month**:
  - TAC: N=54, SRL: N=56
  - P=0.22

- **1 Year**:
  - TAC: N=54, SRL: N=55
  - P=0.12

- **2 Years**:
  - TAC: N=25, SRL: N=30
  - P=0.71

**Conclusion**: No significant difference in the percent with IFTA ≥ 2 was observed between TAC and SRL at 1 and 2 years after conversion.
Effect of Rapamycin Conversion on Cancer

- SRL Conversion (n=551)
- CNI Continuation (n=273)

Number of Events per 100 Person-Years of Exposure

P<0.001

- All: 2.1 vs. 6.0
- NMSC: 1.2 vs. 4.3
- AOM*: 1.0 vs. 2.1

P=0.058
Rapamycin in Patients with Skin Cancer

Drug discontinued:
10/64 (15.6%) SRL
3/56 (5%) CNI

Shaded boxes indicate 95% confidence intervals.

Question 4

A 40 year old 3 years after a deceased donor kidney transplant is on tacrolimus, mycophenolate and prednisone 2.5 mg daily. You would consider switching tacrolimus to an mTOR inhibitor for new onset diabetes.

A. Yes
B. No
C. Unsure
Everolimus for CNI Minimization

Free from BPAR, Death, Graft loss, or Loss to follow-up

- Everolimus 3–8ng/mL (N=277)
- Everolimus 6–12ng/mL (N=279)
- MPA (N=277)

*p > 0.100 for everolimus versus MPA at Months 12 and 24

KDIGO

Kidney Disease: Improving Global Outcomes

# Late Conversion from CNI to Everolimus

<table>
<thead>
<tr>
<th></th>
<th>EVR + CNI Elimination (N=127)</th>
<th>EVR + CNI Minimizaton (N=144)</th>
<th>Controls (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR</td>
<td>7 (5.5%)</td>
<td>8 (5.6%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>72 (56.7%)*</td>
<td>78 (54.2%)</td>
<td>52 (42.3%)</td>
</tr>
<tr>
<td>Proteinuria &gt; 3.5 g/L</td>
<td>10 (7.9%)</td>
<td>15 (10.4%)</td>
<td>5 (4.1%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36 (28.3%)*</td>
<td>34 (23.6%)*</td>
<td>11 (8.9%)</td>
</tr>
<tr>
<td>mGFR (mL/min/1.73m²)</td>
<td>48.0±22.0</td>
<td>46.6±21.1</td>
<td>46.0±20.4</td>
</tr>
</tbody>
</table>

*P<0.05 v. Controls
A 32 year old with no rejection 6 months after a living donor kidney transplant, develops diarrhea. He is on tacrolimus, mycophenolate mofetil (MMF) and prednisone. Evaluation for treatable causes of diarrhea is negative. You would:

A. Reduce the dose of MMF
B. Change MMF to EC-mycophenolate sodium
C. Change MMF to azathioprine
D. Use symptomatic treatment only
Effect on GI Symptoms of Conversion to Enteric-Coated Mycophenolate Sodium

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EC-MPS (N=199), n (%)</th>
<th>MMF (N=197), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one GI AE*</td>
<td>77 (38.7)</td>
<td>91 (46.2)</td>
<td>0.1545</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>27 (13.6)</td>
<td>31 (15.7)</td>
<td>0.5719</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (11.1)</td>
<td>19 (9.6)</td>
<td>0.7420</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19 (9.5)</td>
<td>17 (8.6)</td>
<td>0.8616</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (5.5)</td>
<td>23 (11.7)</td>
<td>0.0320</td>
</tr>
<tr>
<td>Flatulence</td>
<td>11 (5.5)</td>
<td>19 (9.6)</td>
<td>0.1325</td>
</tr>
<tr>
<td>Eructation</td>
<td>9 (4.5)</td>
<td>20 (10.2)</td>
<td>0.0348</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>9 (4.5)</td>
<td>18 (9.1)</td>
<td>0.0754</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>11 (5.5)</td>
<td>14 (7.1)</td>
<td>0.5426</td>
</tr>
<tr>
<td>Intestinal functional disorder</td>
<td>10 (5.0)</td>
<td>14 (7.1)</td>
<td>0.4079</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>13 (6.5)</td>
<td>9 (4.6)</td>
<td>0.5115</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (3.5)</td>
<td>15 (7.6)</td>
<td>0.0829</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (3.0)</td>
<td>11 (5.6)</td>
<td>0.2258</td>
</tr>
</tbody>
</table>

* A patient with multiple occurrences of an AE is counted only once in the AE category for that treatment.
Intensified Mycophenolate

- 2 open-label RCTs (N=441)
  - EC-MMF
  - 2w 2880/d; 4w 2160/d then 1440/d
  - Standard 1440/d
- Other:
  - IL2-RA (74%), CsA, steroids
- AEs causing dose reduction:
  - Intensified: 67 (31.5%)
  - Standard: 45 (20.5%) P=0.011

Incidence of BPAR

13.8% v. 19.3% P<0.034

AUC-12

Intensified, n
Standard, n
Day 3 41 41
Day 10 33 38
Day 21 26 32
Day 42 30 29
Day 56 26 31
Day 87 24 30
## Conversion to Once Daily Tacrolimus

<table>
<thead>
<tr>
<th>Event at 12 Months</th>
<th>Once Daily (N=162)</th>
<th>Twice Daily (N=162)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy failure*</td>
<td>4 (2.5%)</td>
<td>4 (2.5%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>20 (12.3%)*</td>
<td>4 (2.5%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Adverse events</td>
<td>135 (82.7%)</td>
<td>133 (81.6%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>36 (22.2%)</td>
<td>26 (16%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

*Death, graft failure, locally read biopsy-proven acute rejection, or loss to follow-up

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Kidney Disease: Improving Global Outcomes

Once v. Twice Daily Tacrolimus Adherence

Percentage of patients with correct dosing

Number of Days since Randomization

QD (N=145)

BID (N=74)

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Kidney Disease: Improving Global Outcomes

Key RCT Results since the KDIGO Guideline

Alemtuzumab: similar to rATG, possibly less expensive
Belatacept: role unclear
Rapamycin: role unclear except to prevent skin cancer
Everolimus: similar to rapamycin
Enteric-coated mycophenolate sodium: role unclear
Intensified mycophenolate: role unclear
Once daily tacrolimus: may improve adherence
New Immunosuppression Horizons

- “Golden Era” of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- Recent Randomized Trials
- New Drug Development
A 40 year old 3 years after a deceased donor kidney transplant on low-dose tacrolimus, mycophenolate and prednisone 2.5 mg daily, develops decreasing eGFR 60 to 50 mL/min/1.73 m² over 12 months. Biopsy shows Banff Grade 2 interstitial fibrosis, inflammation in areas of fibrosis, C4d(-), and arteriolar hyalinosis. A single DSA is positive in low titer. This is most likely:

A. Chronic antibody-mediated rejection
B. CNI toxicity
C. Non-adherence
D. A combination of the above
New Immunosuppression Horizons
# Tofacitinib versus CsA

<table>
<thead>
<tr>
<th>Complication</th>
<th>CsA (N=109)</th>
<th>CP MI (N=106)</th>
<th>CP LI (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR at Month 12</td>
<td>18.8%</td>
<td>17.4%</td>
<td>15.4%</td>
</tr>
<tr>
<td>mGFR (mL/min)</td>
<td>53.9</td>
<td>64.6*</td>
<td>64.7*</td>
</tr>
<tr>
<td>CMV disease</td>
<td>4.5%</td>
<td>19.5%*</td>
<td>13.3%*</td>
</tr>
<tr>
<td>PTLD</td>
<td>0</td>
<td>2#</td>
<td>1</td>
</tr>
</tbody>
</table>

*p<0.05 vs. CsA; #2 more cases of PTLD after 12 mo.
Sotrastaurin with Tacrolimus Minimization

*BPAR, graft loss, death or lost to follow-up.
Sotrastaurin versus Tacrolimus

*BPAR, graft loss, death or lost to follow-up at month 3.
### Alefacept Phase II RCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (N=79)</th>
<th>A+Low Tac (N=77)</th>
<th>A+Tac (N=75)</th>
<th>A(qow)+Low Tac (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR (%)</td>
<td>12.7</td>
<td>26.3*</td>
<td>18.8</td>
<td>16.7</td>
</tr>
<tr>
<td>CD4+ T memory (cells/mm³)</td>
<td>538.6</td>
<td>335.2*</td>
<td>330.9*</td>
<td>268.8*</td>
</tr>
<tr>
<td>CD8+ T memory (cells/mm³)</td>
<td>146.3</td>
<td>84.8*</td>
<td>92.0*</td>
<td>56.2*</td>
</tr>
</tbody>
</table>

*P<0.05 versus control
Alefacept Phase II RCT

![Graph showing event rate over days following transplant for Alefacept and Placebo groups.]

- **Event rate (%)**
  - Alefacept: 10.6%
  - Placebo: 6.7%
- **Days following transplant**
  - Patients at risk, n
  - Alefacept: 105, 100, 95, 94, 93, 92, 91, 90, 90, 90, 90, 89, 88, 85
  - Placebo: 107, 103, 99, 99, 98, 98, 98, 97, 97, 97, 97, 96, 95
- **p = 0.309**

Rituximab Induction

![Graph showing rejection-free survival over days after treatment for Rituximab and Daclizumab treatments.](image)

- Rituximab (N=5/6)
- Daclizumab (N=1/7)

P = 0.01

Days after Treatment

Kidney Disease: Improving Global Outcomes

## Rituximab Induction

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (N=68)</th>
<th>Placebo (N=68)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure*</td>
<td>10 (14.7%)</td>
<td>14 (20.6%)</td>
<td>0.348</td>
</tr>
<tr>
<td>at 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPAR at 6 months</td>
<td>8 (11.6%)</td>
<td>12 (17.6%)</td>
<td>0.317</td>
</tr>
</tbody>
</table>

*Acute rejection, graft loss, or death during the first 6 months
## Rituximab Induction

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (N=138)</th>
<th>Placebo (N=142)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR at 6 mo.</td>
<td>15.9%</td>
<td>21.8%</td>
<td>0.15</td>
</tr>
<tr>
<td>BPAR at 6 mo. in N=62 with PRA&gt;6 or re-transplant</td>
<td>17.9%</td>
<td>41.1%</td>
<td>0.039</td>
</tr>
<tr>
<td>Patient survival at 24 mo.</td>
<td>92.3%</td>
<td>92.8%</td>
<td>0.87</td>
</tr>
<tr>
<td>Graft survival at 24 mo.</td>
<td>88.7%</td>
<td>87.7%</td>
<td>0.93</td>
</tr>
</tbody>
</table>

M. van den Hoogen, et al. ATC 2013 (abstract 266.1)
# Systematic Review of AMR Treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Action</th>
<th>Evidence supporting the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis (PP)</td>
<td>Decrease the titer and block the effect of DSA</td>
<td>Low, benefit not consistently demonstrated</td>
</tr>
<tr>
<td>Immunoabsorption (column)</td>
<td>Decrease the titer of DSA</td>
<td>Low, seems beneficial</td>
</tr>
<tr>
<td>IVIG</td>
<td>Decrease the titer and block the effect of DSA</td>
<td>Very low</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Decrease production of DSA</td>
<td>Very low</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells</td>
<td>Very low</td>
</tr>
<tr>
<td>Anti-thymocyte preparations</td>
<td>Reduce production of DSA by decreasing Helper T cells, suppression of T cells</td>
<td>Very low</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Block complement activation resulting from DSA activation</td>
<td>Very low</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Block the effect and decrease production of DSA, suppression of T cells</td>
<td>Very low</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Decrease production of DSA</td>
<td>Very low</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Decrease production of DSA</td>
<td>Very low</td>
</tr>
<tr>
<td>Deoxyspergualin</td>
<td>Decrease production of DSA, suppression of T cells</td>
<td>Very low</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Decrease production of DSA</td>
<td>Very low</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Decrease production of DSA, Suppression of T cells</td>
<td>Very low</td>
</tr>
</tbody>
</table>
Rituximab Treatment of Acute Cellular Rejection with B-Cell Infiltrates

- Rituximab in acute cellular tubulointerstitial rejection with B-cell infiltrates (RIACT).
- Randomized, double-blind, placebo-controlled, parallel group Phase III study.
- Addition to standard treatment with steroids
- Endpoint: 1-year kidney function
- N=180
Ongoing Phase II Bortezomib Trials

• Prevention of AMR in sensitized patients
• Treatment of late AMR
Ongoing Phase II Eculizumab Trials

• Prevention of AMR in sensitized patients
• Prevention of AMR in XM(+) patients
• Treatment of acute AMR
• Treatment of chronic AMR
• World's most expensive drug?
  (Matthew Herper, Forbes, Feb. 22, 2010)
Promising Pipeline?

**Tofacitinib**: higher rate of PTLD versus CsA

**Sotrastaurin**: more rejection versus tacrolimus

**Alefacept**: more rejection versus tacrolimus

**Rituximab**: phase III induction & AMR treatment trials

**Bortezomib**: phase II induction & AMR treatment trials

**Eculizumab**: phase II induction & AMR treatment trials
New Immunosuppression Horizons

- “Golden Era” of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- Recent Randomized Trials
- New Drug Development