UCMC Kidney Transplant Guidelines
Treatment of Biopsy Proven Acute Cellular Rejection
For Recipients on Belatacept-based Immunosuppressive Regimens

Clinical experience suggests that recipients on a belatacept-based regimen may require tacrolimus (Prograf®) to fully resolve a rejection episode. The goal of adding a tacrolimus (Prograf®) is to **reverse histologic evidence of rejection** while continuing the regular belatacept dosing schedule. Initiation of tacrolimus (Prograf®) will be tailored per the severity of the rejection as described in the tables below.

I. Treat episodes of rejection according to Banff classification as described in table below
II. For ALL episodes, obtain MPA AUC and then adjust mycophenolate mofetil (Cellcept®) dose per MPA Monitoring Guidelines.
III. Repeat biopsy depends on response to treatment and current treatment
   a. If steroids used: repeat biopsy if SCr increases during treatment or no improvement at 7 days
   b. If CNI used: repeat biopsy as per dosing guidelines for CNI therapy and before stopping CNI
IV. All patients experiencing a recurrent rejection of Banff 1997 (updated 2007) IA or greater should receive rabbit antithymocyte globulin (Thymoglobulin®) and enhanced immunosuppression. Consider transitioning patient to CNI-based regimen and/or adding maintenance corticosteroid therapy
V. If possible, patients should have their labs drawn at UCMC or at West Chester Hospital in order to expedite laboratory turnaround times

TREATMENT OF REJECTION BASED ON BANFF GUIDELINES

BORDERLINE REJECTION

Enhance baseline immunosuppression and rebiopsy at 7-10 days ; if SCr worsens, repeat biopsy sooner

IA REJECTION - Banff 1997 (updated 2007)

First Line: corticosteroids

Methylprednisolone 500mg IV x 3 doses (Days 1-3)
Follow with oral prednisone taper:

Day	4	5	6	7	8	9	10	11 +
Prednisone dose (mg)	200	160	120	80	40	20	10	5

Decision to taper prednisone to less than 5mg daily per physician discretion

Second line: Tacrolimus (Prograf®)

Tacrolimus (Prograf®) 0.1mg/kg/dose twice daily
- Total dose of 0.2mg/kg/day
- Planned duration of 28 days

Refer to dosing and biopsy guidelines below for target troughs and biopsy time points

Third line: Rabbit antithymocyte globulin (Thymoglobulin®)

Rabbit antithymocyte globulin (Thymoglobulin®) 1.5mg/kg/day over 4-6 hours
Premedicate with:
- Diphenhydramine (Benadryl®) 25mg
- Acetaminophen (Tylenol®) 650mg
- Corticosteroids
  - 1st dose: methylprednisolone 250 mg
  - 2nd dose: methylprednisolone 125 mg
  - No steroids thereafter unless infusion reactions to rabbit antithymocyte globulin (Thymoglobulin®)

Target 7 days of CD3 suppression (absolute CD3 count < 25 cells/μL)[1]
- Order scheduled CD3 counts (via transplant monitor panel)

[1]If CD3 count is unavailable, can target absolute lymphocyte count <70 /μL

Note: if lymphocyte-depleting therapy is used to treat rejection, the prophylactic medications must be recycled. Restart PCP and antiviral prophylaxis as per current post-transplant infectious prophylaxis guidelines

<table>
<tr><th colspan="2">IB REJECTION - Banff 1997 (updated 2007)</th></tr>
<tr><td rowspan="2">First line:
tacrolimus (Prograf®)
AND
corticosteroids</td><td>Tacrolimus (Prograf®) 0.1mg/kg/dose twice daily
• Total dose of 0.2mg/kg/day
• Planned duration of 28 days
Refer to dosing and biopsy guidelines below for target troughs and biopsy time points</td></tr>
<tr><td>Methylprednisolone 500mg IV x 3 doses (Days 1-3)
Follow with oral prednisone taper:
<table><tr><td>Day</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11 +</td></tr><tr><td>Prednisone dose (mg)</td><td>200</td><td>160</td><td>120</td><td>80</td><td>40</td><td>20</td><td>10</td><td>5</td></tr></table>Decision to taper prednisone to less than 5mg daily per physician discretion</td></tr>
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Rabbit antithymocyte globulin (Thymoglobulin®)</td><td>Rabbit antithymocyte globulin (Thymoglobulin®) 1.5mg/kg/day over 4-6 hours
Premedicate with:
• Diphenhydramine (Benadryl®) 25mg
• Acetaminophen (Tylenol®) 650mg
• Corticosteroids
○ 1st dose: methylprednisolone 250 mg
○ 2nd dose: methylprednisolone 125 mg
○ No steroids thereafter unless infusion reactions to rabbit antithymocyte globulin (Thymoglobulin®)
Target 7-10 days of CD3 suppression (absolute CD3 count < 25 cells/μL)[1]
• Order scheduled CD3 counts (via transplant monitor panel)</td></tr>
<tr><th colspan="2">IIA or greater REJECTION - Banff 1997 (updated 2007)</th></tr>
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tacrolimus (Prograf®), rabbit antithymocyte globulin (Thymoglobulin®)
AND
corticosteroids</td><td>Tacrolimus (Prograf®) 0.1mg/kg/dose twice daily
• Total dose of 0.2mg/kg/day
• Planned duration of 28 days
Refer to dosing and biopsy guidelines below for target troughs and biopsy time points</td></tr>
<tr><td>Rabbit antithymocyte globulin (Thymoglobulin®) 1.5mg/kg/day over 4-6 hours
Premedicate with:
• Diphenhydramine (Benadryl®) 25mg
• Acetaminophen (Tylenol®) 650mg
• Corticosteroids: as per steroid taper below
Target CD3 suppression (absolute CD3 count < 25 cells/μL)[1]:
• Banff IIA: 10 days
• Banff ≥ IIB: 14 days
• Order scheduled CD3 counts (via transplant monitor panel)</td></tr>
<tr><td>Steroid taper:
<table><tr><td>Day</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9 +</td></tr><tr><td>Methylprednisolone IV dose (mg)</td><td>250</td><td>250</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td></tr><tr><td>Prednisone dose (mg)</td><td>--</td><td>--</td><td>160</td><td>120</td><td>80</td><td>40</td><td>20</td><td>10</td><td>5</td></tr></table>Decision to taper prednisone to less than 5mg daily per physician discretion</td></tr>
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[1]If CD3 count is unavailable, can target absolute lymphocyte count <70 /μL

Note: if lymphocyte-depleting therapy is used to treat rejection, the prophylactic medications must be recycled. Restart PCP and antiviral prophylaxis as per current post-transplant infectious prophylaxis guidelines

Tacrolimus (Prograf®) Dosing and Re-Biopsy Guideline		
Treatment day	**Goal tacrolimus trough (ng/mL)**	**Biopsy**
0		
1-7	12-15	
8-14	12-15	Repeat biopsy after 7 days of exposure to therapeutic tacrolimus (Prograf®) levels*
15-19	10-12	
20-24	6-9	
25-27	3-5	Repeat biopsy to confirm complete histologic reversal of rejection within 3 days prior to tacrolimus withdrawal
28	Discontinue tacrolimus	Tacrolimus can only be discontinued once histological resolution of rejection is confirmed or patient has started an alternative treatment for rejection

*If there is no histological improvement or there is worsening histology at the day 7 biopsy, increase target tacrolimus (Prograf®) trough to 15-20ng/mL and repeat biopsy after 7 days of exposure to therapeutic tacrolimus levels. In the cases of refractory rejections, higher tacrolimus (Prograf®) troughs or longer treatment durations may be required. Targeting higher troughs or prolonging therapy should be made on a case-by-case decision as per physician discretion.