

**Maine Medical Center
Maine Transplant Program
Policies and Procedures
Immunosuppression Policy**

Purpose

Outline the Maine Transplant Program Policy and Procedure on Immunosuppressive Therapy after kidney transplantation.

Policy

Kidney Transplantation is the treatment of choice for end-stage renal disease (ESRD). The risk of allograft rejection is greatest during the first 3 months following transplantation. Induction therapy is that immunosuppression administered peritransplantation that prevents rejection and is necessary for all allogeneic transplant recipients. Such therapy includes intravenous agents that are only given within the first week of transplantation as well as oral agents that are continued long term. The MTP adheres to KDIGO recommendations that antibody induction therapy be provided to all kidney transplant recipients. The most commonly used agent is rabbit antithymocyte globulin.

Procedures

Immunologic Risk Assessment

The following are categorized as criteria that define increased immunologic risk:

1. Regrafts
2. Elevated cPRA > 10%
3. Pre-identified anti-donor HLA antibody
4. Patients with FCXM that is not negative (greater than 30 channel shift T-cell / 50 channel shift B-cell)

Administration of Induction Agents:

The rabbit-derived antithymocyte globulin (Thymoglobulin) is initially dosed as follows:

- 1.5 mg/Kg in the operating room for all recipients, either living or deceased donor recipients

The cumulative target dose is dependent on various factors that include living versus deceased transplant as well as immunologic risk and ranges from 3-6 mg/kg.

Alemtuzumab and Basiliximab are alternate induction agents utilized for patients with either a history of rabbit allergy or in those at risk of worsening myelosuppression associated complications.

Maintenance Immunosuppressive Therapy

Maintenance immunosuppression is the practice of delivering adequate immunosuppression to prevent acute rejection while progressively lowering the trough levels such that the risk of infection, malignancy and chronic allograft nephropathy are minimized (7-12). The MTP initially utilizes a three drug immunosuppressive regimen of steroid, calcineurin inhibitor and anti-metabolite for all patients. The exception to this regimen is the HLA identical living donor recipient with a two-drug regimen of steroid and anti-metabolite. All immunosuppressive tailoring is at the discretion of the Transplant team.

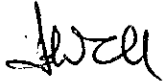
Target Drug Levels

Drug levels are obtained for those agents with unpredictable pharmacokinetics and narrow therapeutic windows. Such agents include tacrolimus, sirolimus, cyclosporine and leflunomide. The target levels are

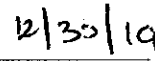
described in the document entitled "Immunosuppressive Drug Level Guidelines," which is available online [here](#).

(<https://mainehealth.org/healthcare-professionals/clinical-resources-guidelines-protocols/maine-transplant-program/policies-procedures>)

The diagnosis and management of rejection is discussed under a separate policy document and is similarly available online.



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Director



Date

Original Date: 2003

Revised Dates: 10/25/07, 6/10/09, 6/6/11, 8/10/12, 1/19/16, 1/29/18, 9/25/18, 4/29/19, 12/20/19

Approved by the Pharmacy and Therapeutics Committee: 9/14/12, 2/12/13, 1/20/14, 2/24/14

Induction Therapy

MTP uses rATG as the standard of care for most patients.

Basiliximab is reserved for patients who are rabbit allergic or are otherwise deemed to be at high risk for serious adverse effects related to rATG.

Alemtuzumab is rarely indicated for those intolerant of either rATG or basiliximab

Thymoglobulin (rATG)

Dose:

Initial dose:

1.5 mg/kg IV
Formulated in NS 1 liter
Infuse over 8 hours
Administer peripherally

Subsequent dose (premedication required):

1.5mg/kg
Formulated in NS 500cc
Infuse over 6 hours
Administer peripherally or via central line

Pre-meds:

Administer usual daily steroid dose 60 min prior to Thymoglobulin.
Diphenhydramine 50 mg PO 60 min before dosing
Acetaminophen 650 mg PO 60 min before dosing

Cumulative Target Dose

3 mg/kg:	Low Immunologic Risk Live Donor Recipients
4.5 mg/kg:	Low Immunologic Risk Deceased Donor Recipients
6 mg/kg:	High Immunologic Risk Transplant Recipients

Selected patients deemed to be increased risk for rATG complications will be considered a priori for basiliximab induction therapy. These include:

Age >70

Primary transplant

cPRA <20%

Hypotension requiring midodrine

Simulect (Basiliximab)

Dose

Initial dose 20 mg IV
Formulated in 250cc NS
Infuse over 30 minutes
Subsequent dose 20 mg IV T+4

Pre-Meds Not required

Alumtuzumab (Campath-1H)

Pre-meds: Administer methylprednisone 500mg IV prior to alemtuzumab

Dose: Single dose intraoperatively 30mg IV x 1
Formulated in NS 100 cc
Infuse over 2 hours
Peripheral or central administration

Rituximab (Rituxan)

Indication: High Immunologic Risk Patients defined as:
1. Low level donor specific antibody on pretransplant testing, or
2. FCXM weak positive

Dose: Rituximab 200mg IV as single peritransplant dose

Premeds: Solumedrol 60mg IV
Benadryl 25mg PO
Acetaminophen 1000mg
PO

Maintenance Immunosuppression

Steroids

Pre-op: Methylprednisolone:
500 mg IV on call to OR

Post-Op: Prednisone 30 mg/day T+1
Prednisone Taper: Reduce dose by 5 mg every 14 days.
Target Maintenance dose: 5 mg/day by 10 weeks.

Mycophenolate Mofetil (MMF, Cellcept®):

Post-op Standard Dose:
MMF 1000 mg PO Q12h

IV Mycophenolate is occasionally given for acute GI intolerance if the latter is expected to resolve rapidly.
Dose is same as PO.

Enteric Coated Mycophenolic Acid (MPA, Myfortic®)

Indication: Patient intolerance of MMF

Dose: 720 mg doses is equimolar with 1000 mg MMF

Management of Myelosuppression

Anemia

Anemia is a frequent complication of immunosuppressive therapy due to myelosuppression. Need to consider other causes such as iron deficiency, bleeding or hemolysis. As post transplant anemia is generally self limiting, ESA therapy is usually not necessary. Consider ESA or transfusion therapy for Hct < 20.

- Leukocyte filtered
- CMV negative blood only for CMV negative recipients of CMV negative donor kidney
- Irradiation is no longer deemed necessary and should not be ordered

Leukopenia

Leukopenia is a frequent complication of immunosuppressive therapy due to myelosuppression

For WBC < 4 reduce medications in the following order:

1. Mycophenolate (MMF)
2. Sirolimus (Rapamune®)
3. Valganciclovir
4. Thymoglobulin

Hold above medications for WBC < 2

Administer G-CSF 5mcg/kg rounded to either 300 or 480 mcg SQ for WBC < 1 or absolute neutropenia (ANC < 500)

Thrombocytopenia

Thrombocytopenia is an infrequent complication of immunosuppressive therapy due to myelosuppression or TMA

For platelets less than 70,000 - reduce medications in the following order

1. Sirolimus
2. Mycophenolate
3. Thymoglobulin

Management of Reduced Immunosuppression

Immunotherapy may be reduced for various reasons. Many such patients can be successfully with dual immunotherapy. However, increased immunologic risk recipients risk rejection under such circumstances. MTP recommends that the third agent be resumed when the underlying reason for discontinuation has been mitigated. **Tacrolimus (Prograf®)**

Dose: Tacrolimus 0.025 mg/kg PO q 12 hrs. (dose at 6 am and 6 pm in hospital)
Levels: Further adjustments in Tacrolimus based upon Tacrolimus whole blood levels:

Time Post-Transplant	Desired WB Tacrolimus Level
< 3 months	10 – 12 ng/ml
3-12 months	7 – 10 ng/ml
> 12 months	3 – 7 ng/ml

Sublingual Tacrolimus:

Indication: Inability to take PO Tacrolimus
A 30% dose reduction is required as liver first phase metabolism is avoided.

Intravenous Tacrolimus:

Indication: Inability to take PO or SL Tacrolimus
A 2/3 dose reduction is required as liver first phase is avoided. The total daily dose is typically divided by 3, made up in 100 ml of NS and administered over 24 hours.

For example, when the PO dose is 6 mg bid: the conversion to IV is to administer 4 mg Tacrolimus in 100 ml NS at 4 ml/hour. Subsequent levels lack diurnal variation. A steady state trough level of approximately 20 mg/ml is desired. This formulation should be avoided whenever possible to avoid nephrotoxicity.

Tacrolimus Extended Release (Tacrolimus XL, Astagraf®)

- May be chosen to minimize frequency of dose administration
- Once daily dosing: Same cumulative dose as twice daily administration if converting from immediate release tacrolimus
- 24-hour trough target levels same as above

Tacrolimus Extended Release (LCPT, Envarsus XR®)

- May be chosen to minimize frequency of dose administration or to minimize impact of tremors
- Once daily dosing: Reduce dose by ~30% if converting from immediate release tacrolimus
- 24-hour trough target levels same as above

Management of Tacrolimus Pharmacokinetics:

- Some patients require high dose tacrolimus to maintain therapeutic levels (defined as a cumulative dose exceeding 10mg/day). This leads to increased costs
- The MTP will consider the concurrent use of CYP 3A/4 inhibitor therapy to reduce dose and cost requirement. For example, concurrent use of diltiazem and tacrolimus.
- This practice is generally to be avoided unless deemed absolutely necessary by the transplant nephrologist and transplant surgeon.

Belatacept (Nulojix®)

Belatacept is a selective T-cell stimulation blocker used to prevent rejection after kidney transplant. Belatacept acts by binding to CD80 and CD86 cells on antigen presenting cells, thus blocking the activation of T lymphocytes.

FDA approved in June 2011 for the prevention of acute rejection in adult patients who have had a kidney transplant. MMC, P&T committee approved belatacept use 10/7/2011 in adult kidney transplant patients who are:

- EBV positive and
- Intolerant to CNI (first line) and m-TOR inhibitor (sirolimus) due to refractory toxicity

Administration

Formulated in NS 100cc
Infused peripherally over 30 minutes

Induction Dose:

0-3 mos
10mg/kg on days 1, 5
10mg/kg on weeks 2, 4, 8, 12
5mg/kg monthly thereafter

Converting from CI or mTORi to Belatacept:

Belatacept often replaces tacrolimus, cyclosporine or sirolimus in traditional protocols. When belatacept was directly compared with these older immunosuppressive agents, similar patient and transplant survival rates were found. However, the profile of adverse effects was quite different. For example, patients treated with belatacept had less hypertension, hyperlipidemia & hyperglycemia, and better kidney function. The downside was an increased rejection risk early after transplantation and an increased risk of post-transplant lymphoproliferative disease in patients who had no antibody to Epstein Barr virus and who were receiving high non-FDA approved doses.

Belatacept Conversion Dosing:

Regardless of initial CI or mTORi therapy, belatacept dosing is as follows:
Belatacept 5mg/kg every 2 weeks for first 2 months (total of 5 doses at q2 week interval) followed by monthly infusions thereafter.

CI/mTORi Cross taper regimen with a view to discontinuation:

Sirolimus:

Sirolimus should continue at the same dose as the dose at the belatacept initiation for 14 days (until second belatacept infusion) at which time it should be stopped.

Tacrolimus IR and ER & Cyclosporine:

Tacrolimus is to be cross-tapered over a 1 month period in following manner:
100% of the dose or target level should continue for first two weeks of belatacept therapy then reduced by 50% for the next two weeks and then it should be stopped.

References:

1. NULOJIX [prescribing information]. Princeton, NJ: Bristol-Myers Squibb.
 2. Lexi-Comp Online™, Hudson, Ohio: Lexi-Comp, Inc.; January 21st, 2014
- Rostaing L, Massari P, Garcia VD, et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clin J Am Soc Nephrol. 2011;6(2):430-9.