Maine Medical Center
Maine Transplant Program
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 at 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 majority of patients. The exception to this regimen is the HLA identical living donor recipient with a two-drug regimen of steroid and anti-metabolite and patients that may be eligible for belatacept based regimen due to CNI toxicity or non-adherence. 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.

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, 10/10/22, 2/17/23, 9/20/23
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
- Formulated in NS 500cc
- Infuse over6 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+3-4

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. Valganciclovir
4. Bactrim

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. Mycophenolate
2. Thymoglobulin

Management of Reduced Immunosuppression

Immunotherapy may be reduced for various reasons. Many such patients can be successfully managed with dual immunotherapy however rejection may be seen in higher immunologic risk patients. MTP recommends that the third agent be resumed when the underlying reason for discontinuation has been mitigated, particularly within the first year post transplant

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 50% dose reduction is required as liver first phase metabolism is avoided.

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®) Based Protocols and Conversions

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.

Indications for CNI Minimization

1. Toxicity
    a. Renal
        i. Acute/Chronic Nephrotoxicity
        ii. TMA
    b. Non-Renal
        i. Neurological
            1. Headache
            2. Tremors
            3. Seizures
            4. PRES syndrome
        ii. Endocrine
            1. Poorly controlled diabetes
        iii. Severe HTN
2. Non-Adherence

<u>Belatacept Therapy Considerations</u>

1. Patients must meet following criteria:
    a. EBV positive serology
    b. No history of lymphoma, PTLD, or hematologic malignancy
    c. No history of HIV
    d. No IV access issues
    e. No transportation limitations

2. Ensure adequate dosing of baseline immunosuppression (with exception of the CNI agent that is being reduced or discontinued) during conversion

3. Patients at higher immunologic risk should be carefully considered prior to conversion

    a. Prior graft loss due to acute rejection
    b. Recent acute rejection (within 3 months)
    c. Banff 97 IIA or higher acute rejection

4. Financial implications of conversion to belatacept for the patient to be assessed and discussed with the patient prior to conversion

IMMEDIATE CONVERSION/CNI WITHDRAWAL RECOMMENDATIONS

- For patients with toxicity necessitating immediate discontinuation of CNI (i.e. TMA)

Belatacept dosing:

Per Package insert:
10mg/kg on days 1, 5
10mg/kg on weeks 2, 4, 8, 12

CNI dosing: Discontinue the first day belatacept is dosed

QUADRUPLE THERAPY IN PATIENTS < 1 YEAR POST-TRANSPLANT

- For patients with significant CNI toxicity or intolerances

Belatacept dosing:

5mg/kg for total of 5 doses at q2 week interval followed by 5mg/kg monthly infusions

CNI dosing: Reduce tacrolimus trough to 5-8 ng/ml for 1 month, then reduce to 3-5 ng/ml for a minimum of 3 months AND until at least 6 months post-transplant. May maintain tacrolimus troughs between 2-4 ng/ml 6-12 months post-transplant and taper tacrolimus off over 3 months after as tolerated.

> 1 YEAR POST-TRANSPLANT CONVERSION RECOMMENDATIONS

- For patients with significant CNI toxicity, intolerance, or who may benefit from long-term CNI avoidance

Belatacept dosing:

5mg/kg for total of 5 doses at q2 week interval followed by monthly infusions

CNI dosing: 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.

Of note, specific induction dosing may vary based on specific clinical scenario and will be determined by Transplant Pharmacist and Transplant Team at the time of belatacept initiation.

Appendix to Immunosuppression Policy

Management of Immunotherapy after Allograft Failure

In spite of improvements in long term patient and graft survival after kidney transplantation, allografts can still fail early (<1 year post surgery) or late (>1 year post surgery) for a variety of reasons not limited to thrombosis, rejection, infection, and chronic allograft nephropathy. Such allograft failures associate with higher risk of patient mortality after dialysis initiation compared with non transplant causes of ESRD driven mostly by infection.

For patients who return to dialysis under these circumstances, there are generally 2 major decisions to make:
1. Withdrawal versus continuing immunotherapy
2. Proceeding with allograft nephrectomy (or not).

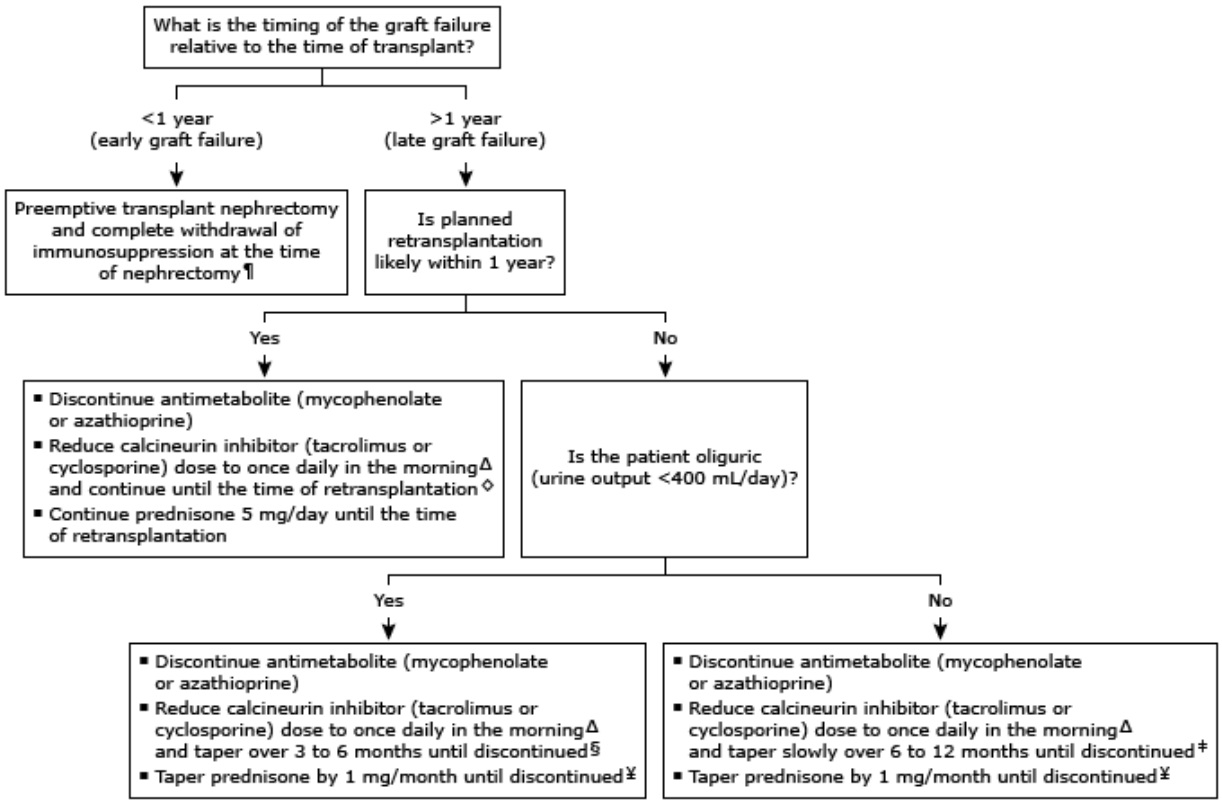
While this document deals with the former, the transplant program is uniquely situated to opine on both questions noting there are pros and cons to each issue.

Risks and Benefits
Potential benefits of immunosuppression withdrawal include:
- Reduced cost
- Reduced risk of immune adverse effects including infection and malignancy
- Reduced risk of non immune adverse effects including neurotoxicity

Potential complications of withdrawing immunosupression include
- Symptomatic rejection
- Secondary adrenal insufficiency
- Loss of residual kidney function
- Allosensitization

Early Graft Failure
Grafts that fail within the first year are generally explanted and immunosuppression and antimetabolite/calcineurin inhibitor/costimulatory blockade is stopped.
Steroid therapy if present for 3 or more months is typically weaned with a view to discontinuation over a period of weeks.

Late Graft Failure
The approach to tapering immunoRx in allografts that fail after a year or more depends on whether the patient is likely to be retransplanted and avoid the risk of allograft nephrectomy and allosensitization.


What is the timing of the graft failure relative to the time of transplant?
<1 year (early graft failure)
>1 year (late graft failure)
Preemptive transplant nephrectomy and complete withdrawal of immunosuppression at the time of nephrectomy ¶
Is planned retransplantation likely within 1 year?
Yes
No
▪ Discontinue antimetabolite (mycophenolate or azathioprine)
▪ Reduce calcineurin inhibitor (tacrolimus or cyclosporine) dose to once daily in the morning Δ and continue until the time of retransplantation ◊
▪ Continue prednisone 5 mg/day until the time of retransplantation
Is the patient oliguric (urine output <400 mL/day)?
Yes
No
▪ Discontinue antimetabolite (mycophenolate or azathioprine)
▪ Reduce calcineurin inhibitor (tacrolimus or cyclosporine) dose to once daily in the morning Δ and taper over 3 to 6 months until discontinued §
▪ Taper prednisone by 1 mg/month until discontinued ¥
▪ Discontinue antimetabolite (mycophenolate or azathioprine)
▪ Reduce calcineurin inhibitor (tacrolimus or cyclosporine) dose to once daily in the morning Δ and taper slowly over 6 to 12 months until discontinued ‡
▪ Taper prednisone by 1 mg/month until discontinued ¥