**Policy: Post-Liver Transplant Rejection Protocol**

**Statement: Affected Department:** Liver Transplant Program

**Vision Strategy:** Patient Care

**Policy Statement:** The Emory Transplant Center’s Post Liver Transplant team will comply with the following protocol in the management of patients who have received a liver transplant.

**Basis:** This policy is necessary to ensure that all patients who are experiencing rejection episodes receive optimal medical care.

**Administrative Responsibility:** Section heads, physicians, practitioners, coordinators and staff are responsible for compliance with this policy.

**Scope/Procedure:**

**I. Acute Cellular Rejection (ACR)**

**A. Diagnosis of ACR**

ACR should be diagnosed by biopsy and correlated with the clinical picture.

**B. ACR**:
Treatment may be initiated with mild to severe rejection as diagnosed on biopsy. The drug of choice for treatment of rejection will be corticosteroids.

**Table 1. Treatment of ACR**

|  |  |  |
| --- | --- | --- |
|  | **First Steroid Cycle** | **Second Steroid Cycle** |
| **Day 1** | Methylprednisolone 500mg IV | Methylprednisolone 500mg IV |
| **Day 2 - 3** | Methylprednisolone 250mg IV | Methylprednisolone 500mg IV |
| **Day 4 - 10** | Prednisone 40mg PO daily | Prednisone 40mg PO daily |
| **Day 11 - 30** | Prednisone 20mg PO daily | Prednisone 20mg PO daily |
| **Day 31** | Prednisone taper at discretion of provider | Prednisone taper at discretion of provider |

\*If there is no response to the first cycle of steroids, the second cycle may be considered.

**Table 2. Prophylaxis after Treatment of ACR**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bacterial Prophylaxis** | **Viral Prophylaxis** | **Fungal Prophylaxis** |
| **Agent** | Sulfamethoxazole/trimethoprim SS PO daily | If CMV D+/R-, valganciclovir 900 mg PO dailyIf other CMV status, acyclovir 400 mg PO TID\* | Nystatin suspension 500,000 units (5mL) swish and swallow four times daily should be considered |
| **Duration** | 6 months | 3 months | 3 months |

\*If receiving acyclovir prophylaxis, CMV PCR should be monitored weekly for 3 months.
Medications should be adjusted for renal dysfunction, with the exception of nystatin.
Please refer to the Antiviral and CMV protocols for more information.

Consideration should also be made to place patients on calcium with vitamin D as well as a bisphosphonate (alendronate) to help prevent osteopenia/osteoporosis in patients on steroid therapy. See concomitant medication protocol and pathway for more information.

**C. ACR Resistant to Steroids:**
ACR that is resistant to steroids as determined by biopsy will be treated with T-cell depleting antibodies. The first line of treatment is Thymoglobulin. Patients treated for ACR should restart their antiviral protocol x 3 months, and anti-bacterial prophylaxis x 6 months. Nystatin s/s for fungal (thrush) prophylaxis should also be considered. Please refer to Table 1, as well as, the Antiviral and CMV protocols for more information.

Thymoglobulin (rabbit anti-thymocyte globulin)

Obtain a CXR PA and lateral within 24 hours of starting Thymoglobulin to evaluate for pulmonary edema.
Usual dose is 1.5mg/kg/day, rounded to the nearest 25mg
Pre-medication

Patients should receive pre-medications for the first 3 doses of Thymoglobulin. Administer the following 30 minutes prior to infusion:

Acetaminophen 650mg PO/PR
Diphenhydramine (Benadryl) 25mg - 50mg PO/IV
Methylprednisolone 125 mg IV x 1 on Day 1, Methylprednisolone 60mg IV on day 2, and methylprednisolone 40mg IV on Day 3 or their standard steroid taper given prior to administration of Thymoglobulin.

Central line administration is preferred

If peripheral administration is necessary, the concentration of Thymoglobulin will be diluted to 0.25mg/ml or less and contain 1000 units of heparin and 20mg of hydrocortisone.
For doses administered via a central line, the duration should be no less than 6 hours for the first dose and no less than 4 hours for subsequent doses as tolerated.
For doses administered via a peripheral line, all doses should be given over no less than 6 hours.

Cytokine release syndrome (CRS)

Monitor for CRS, which may occur with the first several doses. Ensure emergency medications are ordered, including:

Epinephrine 1:1000 IV
Hydrocortisone 100mg IV
Diphenhydramine 50mg IV
Albuterol inhaler

Monitor CBC and LFTs daily. The most common dose limiting side effect in liver transplant patients is thrombocytopenia and/or leucopenia.
If platelets fall below 30 or WBC fall below 2, consider administering half the dose of thymoglobulin. The full dose may also be administered every other day.
Usual duration of thymoglobulin for ACR is 7 to 10 days.

**E. Treatment of Antibody Mediated Rejection (AMR)**
**Plasmapheresis/IVIG**

Consult Transfusion Medicine for plasmapheresis:

Plasmapheresis every other day for a total of 5 therapies.

Order sucrose-free IVIG 100mg/kg IV following first 4 sessions of plasmapheresis (rounded to nearest 5g)

Administer dose over 2 hours

Order sucrose-free IVIG 2g/kg IV following 5th session of plasmapheresis (max dose = 140g, rounded to nearest 5g)

Dose may be split into 2 doses of 1mg/kg IV (max 70g) to be infused on separate days
Begin infusion at 50 ml/hr and double rate every 30 min as tolerated to a max infusion rate of 250 ml/hr

IVIG should be given AFTER plasmapheresis, but prior to Thymoglobulin (if prescribed)
Pre-medicate with acetaminophen 650mg and diphenhydramine 50mg if patient did not receive with plasmapheresis.
Repeat DSA titers prior to the 5th session of plasmapheresis, and again 30 days after administering 2g/kg dose of IVIG.

**High Dose IVIG for Antibody Mediated Rejection**

Order sucrose-free IVIG 2g/kg IV (max dose = 140g, rounded to nearest 5g)

Dose may be split into 2 doses of 1mg/kg IV (max 70g) to be infused on separate days
Begin infusion at 50ml/hr and double rate every 30 min as tolerated to a max infusion rate of 250ml/hr.

Pre-medicate with acetaminophen 650mg and diphenhydramine 50mg
Repeat DSA titers 30 days after administration.

**F. Tacrolimus**
Tacrolimus dosage should be increase to optimize therapy, if indicated. Tacrolimus levels should be monitored on a regular basis after an episode of rejection. Goal trough levels of 8-12ng/ml should be resumed as clinically indicated in the setting of ACR.

**G. Mycophenolate mofetil**
The addition of or increase in dosage of mycophenolate mofetil should be considered in patients experiencing ACR. Doses > 3 grams/day should be divided into a three times a day schedule.

**References**:

Bahra M, et. al. Repeated steroid pulse therapies in HCV-positive liver recipients: significant risk factor for HCV-related graft loss. Transplant Proc. 2005; 37(4): 1700-2.

Gedaly R, et al. Prevalent immunosuppressive strategies in liver transplantation for hepatitis C: results of a multi-center international survey. Transplant Int. 2008;21(9): 867-72.

Burton JR and Rose HR. Acute rejection in HCV-infected liver transplant recipients: the great conundrum. Liver Transplantation. 2006;Suppl 12: S38-S47.

Webster AC et. al. Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systematic review of randomized trial data. Transplantation. 2006: 15;81(7): 953-65.

**Related Policies/Procedures: Anti-Viral Protocol, CMV Protocol**

Approved by: Liver Transplant Leadership Group
Approval Dates: 2/2010, 5/13/2011, 6/8/2012, 7/12/13, 6/11/2014, 5/19/2016

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