

**Outcomes of a slowly tapered low dose steroid regimen for immunosuppression in Hepatitis C Virus (HCV) infected recipients of liver transplants.**

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**SCIENTIFIC ABSTRACT**

**BACKGROUND:** Hepatitis C Virus (HCV) infection is the leading indication for orthotopic liver transplantation (OLT) in the United States according to the United Network of Organ Sharing<sup>i</sup>. Despite the life saving efforts of liver transplantation, HCV recurrence is a universal outcome in HCV infected liver transplant recipients<sup>ii</sup>. Some reports have also indicated that the progression of post transplantation HCV infections may involve a more aggressive and rapid path towards cirrhosis; however, long term outcomes post transplantation have been reported to be similar in OLT recipients with and without HCV infection<sup>iii</sup>. In addition, HCV recurrence is the primary cause of graft failure post transplantation<sup>iv</sup>.

Given the adverse impact associated with HCV recurrence, researchers have attempted to investigate predictive variables associated with recurrence. One such variable that has been implicated is the level of immunosuppression post transplantation, where increased immunosuppression has been associated with negative recurrence outcomes. More specifically, early research has shown that steroid boluses, typically studied in the setting of acute rejection episodes, were associated with a higher rate of negative outcomes in HCV + recipients<sup>v, vi, vii</sup>. Studies have also suggested that long term, slowly tapered steroid treatment may reduce the incidence of developing negative outcomes of HCV recurrence<sup>viii, ix</sup>. Despite the knowledge acquired from these studies, further investigation is merited into the most efficacious steroid regimen, including dosage, frequency and duration, to improve outcomes of HCV recurrence post transplantation. Our study will evaluate the outcomes of our home institution's steroid regimens, including a slowly tapered low dose steroid therapy previously adopted as a standard of care in New York Presbyterian Hospital, Columbia University on January 06, 2006.

**STUDY AIM:** This study aims to evaluate the outcomes of a slowly tapered low dose steroid regimen as a component of immunosuppression post liver transplantation with respect to HCV recurrence in HCV+ recipients of liver transplants.

**STUDY DESIGN:** Retrospective cohort with a historical group comparison.

**DATA COLLECTION:** Data on all adult patients who underwent a liver transplantation- both living donor and deceased donor- at the Center of Liver Disease and Liver Transplantation, New York Presbyterian Hospital from 01/01/2004 to 12/31/07 will be

obtained for this study. Administrative and clinical data, including demographics, reason for transplant, medical management of co-morbid medical diseases, post transplantation immunosuppressive regimen, post transplantation biopsies and post transplantation HCV RNA levels will be collected. The administrative and clinical data collection will be limited to a 12 month pre transplantation period, the transplantation surgery period and a 12 month post transplantation period.

PRIMARY OUTCOME: Liver graft survival, patient survival, and recurrence of HCV as determined by i. histological appearance on liver biopsy at 3, 6 and 12 months post transplantation and/ or ii. peak HCV viral load.

STATISTICAL ANALYSIS: Measures of statistical significance will be performed using Student's t-test and/or  $\chi^2$  test. Multiple logistic regressions will be used to analyze secondary outcomes if applicable.

STUDY PROCEDURE: As this is a retrospective cohort study no procedure will take place during the time of investigation.

STUDY DRUG: As this is a retrospective cohort study no drug will be used during the time of investigation.

MEDICAL DEVICE: As this is a retrospective cohort study no medical device will be used during the time of investigation.

STUDY QUESTIONNAIRES: As this is a retrospective cohort study no questionnaires will be used during the time of investigation.

RECRUITMENT OF SUBJECTS: Not applicable.

CONFIDENTIALITY OF STUDY DATA: Data will be collected from paper and electronic medical records, which are protected by standard privacy mechanisms adopted by Columbia University Medical Center. Data collection will involve de-identification to adhere to confidentiality.

POTENTIAL CONFLICTS OF INTEREST: None.

POTENTIAL RISK: As this is a retrospective study of clinical data, this study causes minimal risk to the participants. The potential risk of unintended breach of privacy does exist. However, all precautions will be taken to minimize this risk.

POTENTIAL BENEFITS: None.

LOCATION OF STUDY: Columbia Presbyterian Medical Center.

### **Lay Abstract:**

Hepatitis C Virus (HCV) infection is the leading indication for orthotropic liver transplantation (OLT) in the United States according to the United Network of Organ Sharing<sup>x</sup>. Despite the life saving efforts of liver transplantation, HCV recurrence is a universal outcome in HCV infected liver transplant recipients<sup>xi</sup>. This study proposes that low dose slowly tapered steroid regimen post transplantation will have better outcomes with respect to Hepatitis C recurrence compared to previously implanted steroid protocols that used higher dosages with a shorter tapered period.

This study will examine patient information via previous medical records of all patients who underwent a liver transplantation- both living donor and deceased donor- at the Center of Liver Disease and Liver Transplantation, New York Presbyterian Hospital from 01/01/2004 to 12/31/06 will be obtained for this study. Administrative and clinical data will be gathered for review and analysis. The administrative and clinical data collection will be limited to a 12 month pre transplantation period, the transplantation surgery period and a 12 month post transplantation period. Results will then be statically analyzed.

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<sup>i</sup> [www.unos.org](http://www.unos.org)

<sup>ii</sup> Wright TL, Donegan E, Hsu HH, Ferrel L, Lake JR, et al. Recurrent and Acquired Hepatitis C Viral Infection in Liver Transplant Recipients. *Gastroenterology* 1992 Jul; 103 (1): 317-322.

<sup>iii</sup> Gane EJ, Portmann BC, Naoumov NV, Smith HM, Underhill JA, et al. Long Term Outcome of Hepatitis C Infection After Liver Transplantation. *New England Journal of Medicine*. 1996 Mar; 334 (13): 815-820.

<sup>iv</sup> Verna, EC, Brown, RS Jr. Hepatitis C Virus and Liver Transplantation. *Clinical Liver Disease* 2006; 10:919.

<sup>v</sup> Sheiner PA, Schwartz ME, Mor E, Schluger LK, Theise N et al. Severe or Multiple Rejection Episodes are Associated with Early Recurrence of Hepatitis C After Orthotropic Liver Transplantation. *Hepatology* 1995 Jan; 21(1): 30-34.

<sup>vi</sup> Gane EJ, Naoumov NV, Qian KP, Mondelli MU, Maertens G et al. A Longitudinal Analysis of Hepatitis C Virus Replication Following Liver Transplantation. *Gastroenterology* 1996 110(1): 167-177.

<sup>vii</sup> Berenguer M, Prieto M, Cordoba J, Rayon JM, Carrasco D, et al. Early Development of Chronic Hepatitis in Recurrent Hepatitis C Virus Infection After Liver Transplantation: Association with Treatment of Rejection. *Journal of Hepatology* 1998 May; 28 (5): 756-763.

<sup>viii</sup> Brillanti S, Vivarelli M, De Ruvo N, Aden AA, Camaggi V, et al. Slowly Tapering Off Steroids Protects the Graft Against Hepatitis C Recurrence After Liver Transplantation. *Liver Transplantation* 2002 Oct; 8(10):884-888.

<sup>ix</sup> Berenguer M, Aguilera V, Prieto M, San Juan F, Rayon JM, et al. Significant Improvement in the Outcome of HCV- Infected Transplant Recipients by Avoiding Rapid Steroid Tapering and Potent Induction Immunosuppression. *Journal of Hepatology* 2006; 44: 717-722.

<sup>x</sup> [www.unos.org](http://www.unos.org)

<sup>xi</sup> Wright TL, Donegan E, Hsu HH, Ferrel L, Lake JR, et al. Recurrent and Acquired Hepatitis C Viral Infection in Liver Transplant Recipients. *Gastroenterology* 1992 Jul; 103 (1): 317-322.