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Perioperative Ledipasvir-Sofosbuvir for HCV in Liver-Transplant Recipients

Josh Levitsky

Elizabeth C. Verna

Jacqueline G. O'Leary

Natalie H. Bzowej

D Moonka
Henry Ford Health, DMOONKA1@hfhs.org

See next page for additional authors

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Authors

Josh Levitsky, Elizabeth C. Verna, Jacqueline G. O'Leary, Natalie H. Bzowej, D Moonka, Robert H. Hyland, Sarah Arterburn, Hadas Dvory-Sobol, Diana M. Brainard, John G. McHutchison, and Norah A. Terrault

nonindustry-funded studies (45% and 41%, respectively; P=0.88 by chi-square test).

In randomized, controlled trials in critical care medicine that were published in the ICMJE journals with the highest impact factor, a substantial proportion of trials do not produce secondary publications. Because established trial groups are more likely to publish secondary analyses than independent groups, this difference may represent a missed opportunity in advancing scientific discovery and hypothesis generation that could be addressed through responsible data sharing. There appears to be a considerable delay between the publication of original and secondary analyses. We submit that these observations be taken into consideration in developing guidelines for data sharing to maximize opportunities and benefits for primary and secondary investigators. (Our database will be made available 6 months after the publication of this letter.)

Mahesh Ramanan, F.C.I.C.M.
Redcliffe Hospital
Brisbane, QLD, Australia

John Myburgh, Ph.D., F.C.I.C.M.
George Institute for Global Health
Sydney, NSW, Australia

Balasubramanian Venkatesh, M.D., F.C.I.C.M.
University of Queensland
Brisbane, QLD, Australia
bmvenkat@bigpond.net.au

and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Perioperative Ledipasvir–Sofosbuvir for HCV in Liver-Transplant Recipients

TO THE EDITOR: Hepatitis C virus (HCV) infection continues to be the most frequent indication for liver transplantation, but recurrence of infection is nearly universal in patients who are viremic at the time of transplantation.[1] Direct-acting antiviral agents (DAAs) have been shown to be effective in treating recurrent HCV infection[2,3] but have not been tested in preventing reinfection at the time of liver transplantation. Because HCV RNA levels fall precipitously after liver transplantation owing to removal of the liver, the immediate perioperative period before rebound of viremia represents a unique opportunity to cure HCV infection.[4] We hypothesized that a DAA regimen shorter than the standard 12 to 24 weeks starting immediately before the transplantation might prevent reinfection of the new graft.

We conducted an open-label, multicenter, phase 2 study (ClinicalTrials.gov number, NCT02350569) involving wait-listed patients with chronic HCV genotype 1 infection who were undergoing a first liver transplantation from an HCV-negative donor. Patients who had received previous DAA treatment or who had a creatinine clearance of less than 40 ml per minute at the time of transplantation were excluded. A total of 37 patients were screened, and 16 with a median unadjusted Model for End-Stage Liver Disease score of 13 (on a scale from 6 to 40, with higher scores indicating more advanced liver disease) were enrolled (Fig. S1 and Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Patients received a single dose of ledipasvir (90 mg)–sofosbuvir (400 mg) the day they arrived at the hospital for transplantation and once daily for 4 weeks postoperatively. The primary efficacy end point was a sustained virologic response 12 weeks after the end of the 4-week treatment. Deep sequencing of HCV NS5A

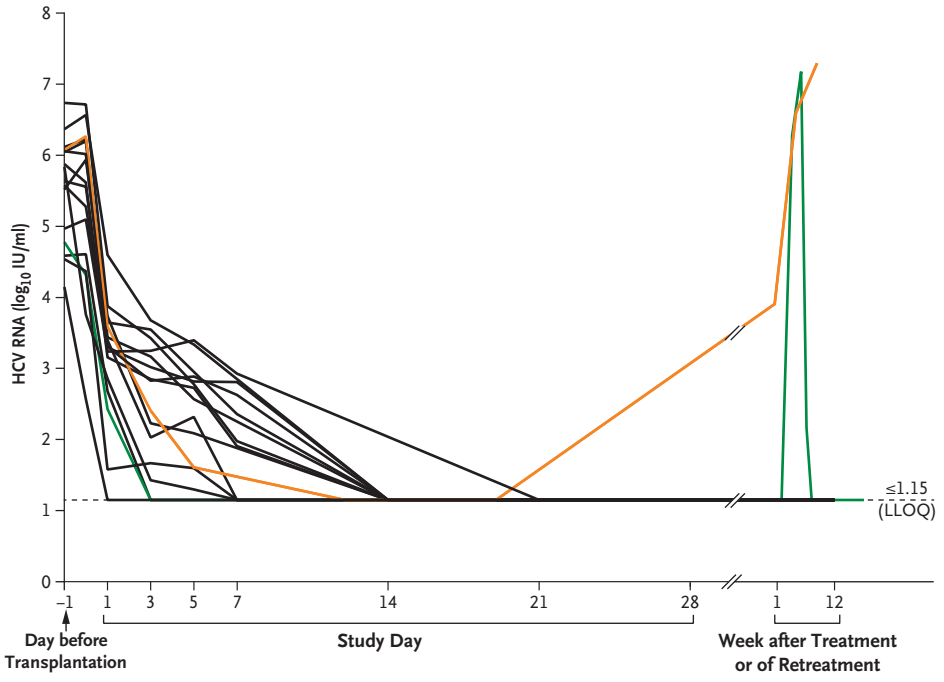

Figure 1. Hepatitis C Virus (HCV) RNA Levels from Day –1 to Post-Treatment Week 12.

The black curves represent the patients who had a sustained virologic response 12 weeks after the end of the 4-week treatment. The green curve represents a patient who had a relapse after initial treatment and had a sustained virologic response after 12 weeks of retreatment. The orange curve represents a patient who discontinued treatment on day 5 of the study owing to predefined stopping criteria. LLOQ denotes the lower limit of quantification.

and NS5B was performed for all recipients at baseline.

Figure 1 shows HCV RNA levels from day –1 to the end of study. The rate of sustained virologic response for the 4-week course was 88% (Table S2 in the Supplementary Appendix). One patient had a relapse after the 4 weeks, but a sustained virologic response was achieved after retreatment with 12 weeks of ledipasvir–sofosbuvir per the study protocol, leading to an overall cure in 15 of the 16 patients (94%). This patient had three NS5A resistance-associated substitutions at study enrollment. One patient discontinued treatment after the creatinine clearance fell below a predefined threshold of 30 ml per minute on day 5. Overall, 88% of the patients had adverse events after liver transplantation, and 31% had serious adverse events (Tables S3 and S4 in the Supplementary Appendix). No patient discontinued treatment owing to an adverse event, had graft loss, or died.

In this trial of preemptive therapy in HCV-positive patients undergoing liver transplantation, a 4-week course of perioperative ledipasvir–sofosbuvir led to a high rate of sustained virologic response, suggesting that it may be an effective approach for preventing HCV recurrence. The only patient with a virologic relapse had NS5A resistance at baseline and had a response to an additional 12 weeks of therapy, suggesting that baseline resistance testing may guide the need for standard courses of therapy. This new perioperative approach needs to be tested in different populations, such as repeat or combined organ recipients and patients with previous DAA treatment failures, and in those with advanced renal failure (other DAAs). In addition, there may be an opportunity to test modifications of this approach in liver or other solid organ recipients being offered HCV-positive organs as a way to increase the donor pool and number of transplants.

Josh Levitsky, M.D.
Northwestern University
Chicago, IL
jlevitsk@nm.org

Elizabeth C. Verna, M.D.
Columbia University
New York, NY

Jacqueline G. O'Leary, M.D., M.P.H.
Baylor University
Dallas, TX

Natalie H. Bzowej, M.D.
Ochsner Clinical Foundation
New Orleans, LA

Dilip K. Moonka, M.D.
Henry Ford Hospital
Detroit, MI

Robert H. Hyland, D.Phil.
Sarah Arterburn, M.S.
Hadas Dvory-Sobol, Ph.D.
Diana M. Brainard, M.D.
John G. McHutchison, M.D.
Gilead Sciences
Foster City, CA

Norah A. Terrault, M.D., M.P.H.
University of California, San Francisco
San Francisco, CA

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The symposium, along with a workshop and public forum, will be held in Miami Beach, FL, Jan. 14 and 15. It is presented by the Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center.

Contact MCI Symposium 2017, c/o World Events Forum, 1631 Whitcomb Ave., Des Plaines, IL 60018; or call (224) 938-9523; or e-mail meetings@worldeventsforum.com; or see http://www.mcisymposium.org.

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