Open Access

OBM Hepatology and Gastroenterology

LIDSEN Publishing Inc.

Review

Can HCV Viremic Organs Be Used in Liver Transplantation to HCV Negative Recipients?

Haris Muhammad [1], Muhammad Baraa Hammami [2], Peng-Sheng Ting [2], Cem Simsek [2], Behnam Saberi [3], Ahmet Gurakar [2 *]

1. Department of Medicine, Greater Baltimore Medical Center, MD, USA; E-Mail: drharismuhammad@gmail.com
2. Division of Gastroenterology and Hepatology, Transplant Hepatology, Johns Hopkins University School of Medicine Baltimore, MD, USA; E-Mails: mhammam2@jhmi.edu; brian.ting@jhmi.edu; cemsimsek90@gmail.com; aguraka1@jhmi.edu
3. Division of Liver Diseases Icahn School of Medicine at Mount Sinai, New York, NY, USA; E-Mail: behnam.saberi@mssm.edu

* **Correspondence:** Ahmet Gurakar; E-Mail: aguraka1@jhmi.edu

Academic Editor: Chung-Feng Huang

Special Issue: Unmet Need in the Management of Chronic Hepatitis C

OBM Hepatology and Gastroenterology
2020, volume 4, issue 2
doi:10.21926/obm.hg.2002046

Received: February 02, 2020
Accepted: April 21, 2020
Published: April 24, 2020

Abstract

Liver transplantation has steadily increased worldwide resulting in a large number of patients on the waiting list. Due to the opioid epidemic in the US, the pool of Hepatitis C seropositive donors increased significantly in recent years. Direct acting antivirals played an instrumental role in making liver transplantation with hepatitis C positive allograft an acceptable option. Although hepatitis C positive liver transplantation to hepatitis C positive recipients is a common practice, there is limited data and agreement on hepatitis C positive liver transplant to hepatitis C negative recipient. Thus, we review the current literature on this topic.

Keywords
Direct Acting Antiviral (DAA), Hepatitis C virus-positive donor, Hepatitis C virus-negative recipient, Nucleic Acid Testing (NAT), Sustained Virologic Response (SVR)

1. Introduction

Hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma and can eventually lead to the need of liver transplantation (LT) [1], which is considered the only curative and lifesaving option. The median wait time in the United States for an LT is 11.3 months; consequently, mortality while on the waitlist is remarkably high [2]. Due to recent surge in opioid use which correlates with intravenous drug abuse, there has been a rise in HCV seropositive donors. Sustained virologic response (SVR) is achieved when HCV ribonucleic acid (RNA) is no longer detectable 12 weeks after completion of treatment and highly correlates with decreased liver-related morbidity and mortality [3, 4]. Historically, HCV recurrence following liver transplant is almost universal, resulting in cirrhosis, graft loss, and re-transplantation. A subset of patient may develop fibrosing cholestatic hepatitis that may progress to rapid graft failure with high mortality [5]. Newer drugs that act on the steps involved in viral replication have led to the availability of several oral HCV treatment regimens [6, 7]

In the interferon (IFN) era, viral eradication led to improved clinical and histological outcomes (reduction in portal pressure, regression of fibrosis, and resolution of clinical decompensations in cirrhotic patients [8, 9] .However, IFN based therapies correlated with decreased rate of SVR and an increased rate of treatment termination due to adverse events [10]. Fortunately, the introduction of direct-acting antivirals (DAAs) has completely changed treatment of HCV infection. Randomized control trials and real-life cohort studies based on HCV-mono-infected LT recipients have shown positive results in terms of efficacy and safety [11].

Table 1 Terminology used for Hepatitis C virus (HCV) infection status [25].

Term	Abbreviation	Definition
HCV seropositive	HCV Ab+	Detectable anti-HCV antibody in serum
HCV seronegative	HCV Ab-	Undetectable anti-HCV antibody in serum
HCV NAT positive	HCV NAT +	Detectable HCV RNA through nucleic acid amplification test in serum
HCV NAT negative	HCV NAT -	Undetectable HCV RNA through nucleic acid amplification test in serum

2. HCV Positive Liver Donors

The U.S. opioid epidemic continues to increase, and deaths from opioid misuse increased threefold between 1999 and 2014. Out of 47,055 deaths caused by excess drug use in 2014 in the United States, 28,647 (60.9%) attributed to opioid use. As per the CDC, between 2014 and 2015, the number of natural/semisynthetic opioid deaths increased in males and the age range of deaths in males and females was reported between 25 and 44 years. In 2015, death rates with newer opioids were highest in males aged between 25 and 44 years (8.9 / 100,000), rising 102.3% from 2014 to 2015 [12]. In all common use of opioids has led to a tremendous rise in drug overdose deaths [13].

Goldberg et al reviewed data from the Organ Procurement and Transplantation Network (OPTN) of all deceased donors who donated minimum of 1 organ between January 1, 2003, and December 31, 2014. When comparing the causes of death in these donors, they found out those who lost their life due to drug misuse were majority Caucasian (86.3% vs. 56.3–72.3% compared to other five categories).They were also younger (median age: 31; $p < 0.001$) when compared to donors who expired from cardiovascular causes (median: 47) and stroke (median: 52). These characteristics correlates with the general pattern of population who were not deceased due to drug misuse. The impact of the drug overdose epidemic on organ donation was most evident in the field of liver transplantation. From 2003 to 2014, the absolute number of deceased-donor LT increased by 1000; nearly 40% of the rise was contributed to by patients who died of drug misuse (103 in 2003 vs. 490 in 2014). [14] Thus, there was a rise in the number of donor organs which were younger, however majority of them were not transplanted due to concern of disease transmission including HCV, HIV and HBV. The predicted prevalence of HCV among donors is 8.5% with a potential of 4% of donors who are NAT positive at the time of transplantation [15] Study done by Durand et al reported that prevalence of HCV infection increased from 7.8% in 2000 to 30.0% in 2017 in donor organs who died of drug overdose [16]. Bari et al published a prospective study where HCV positive/NAT negative livers were transplanted to HCV negative recipients (n= 25) resulting in 16%(n=4) HCV transmission to recipients at 11 months follow up. Upon further evaluation it was reported that all donors to these recipients died of opioid overdose [17].

Reinfection of HCV post LT is common, however, the natural pattern of hepatitis C on the liver allograft varies. Natural history of recurrent Hepatitis C is accelerated, with 20% to 40% progressing to cirrhosis within 5 years [18] HCV reinfection strongly correlated with morbidity and mortality in the interferon era. [19] Peg interferon and Ribavirin used for post-transplant HCV recurrence were linked with major adverse effects in addition to low SVR rates. [20] However, with introduction of DAA treatment, the recipients may now be treated with less adverse outcomes. SVR with the current DAA is 95-98% [21]. The use of DAA led to threefold increase in LT from HCV positive to HCV negative recipients between 2015 and 2016 [22]. Therefore, HCV positive livers which have been discarded in high volumes until now, may be used with high success rate, with the DAA agents.

3. Liver Transplantation from HCV Viremic Donor

The number of patients needing LT is rising steadily, whereas the donor pool is stationary. Due to opioid surge, majority of the patients infected with HCV are younger and candidates for liver donation. Therefore, keeping in view the critical shortage there has been an inclination to use less favorable grafts such as HCV positive grafts. As per United Network for Organ Sharing (UNOS) database the organ donor group between 2015 and 2016 was comprised of 93.8% antibody negative and NAT negative (Ab− NAT−), 0.15% antibody negative and NAT positive, 1.8% antibody positive and NAT negative (Ab+ NAT−), 4.2% antibody and NAT positive (Ab+ NAT+) [23]. Therefore, if we include more donors with Ab+, NAT + in the donor pool it will reduce wait time mortality.

Large study done by Northup et al on 934 HCV positive donors suggested that HCV positive liver donors do not increase the mortality risk in HCV positive recipients when compared to HCV negative liver donors [24]. With the introduction of DAAs, there has been improvement in liver transplant outcomes due to increased sustained virologic response (SVR) and less adverse effects.

Ting et al published a retrospective study consisting of 26 hepatitis C seronegative recipients who received hepatitis C seropositive donor livers followed by preemptive antiviral therapy with DAA treatment, defined as initiation of DAA (median 5.3 weeks after LT), after the first positive HCV NAT in LT recipient. All 12 recipients who completed their DAA courses and reached sufficient follow-up for SVR achieved SVR. Out of the 12 recipients who achieved SVR, 1 received Ledipasvir/Sofosbuvir for 12 weeks, 1 received Sofosbuvir/Velpatasvir for 8 days followed by Ledipasvir/Sofosbuvir for 23 weeks and 10 recipients were treated with Glecaprevir/Pibrentasvir for 12 weeks. [25] Wijarnpreecha et al presented a preliminary data of 22 HCV-seronegative LT recipients who received grafts from HCV-seropositive donors (12 NAT positive, 9 NAT negative). DAA was initiated at a median of 28 days (range 6-67) post LT, resulting in undetectable HCV-RNA in all patients by week 8. However, in this ongoing study recipients of NAT positive livers developed acute membranous nephropathy (n=1), biopsy proven acute cellular rejection (n=4) and intraoperative death (n=1). [26]

Chhatwal et al published a paper which was a virtual trial formulated using Markov-based mathematical model, using data from the United Network for Organ Sharing (UNOS). It showed that transplanting liver irrespective of their HCV status when compared to only transplanting HCV negative liver resulted in increase in life span, when MELD >20 and highest when MELD 28. [27]

Bethea et al used the same Markov-based mathematical model and reported that it is cost effective if recipients with MELD ≥ 22 receive any livers rather than waiting for only HCV negative livers [28]. Regional variations on the MELD score for accepting HCV positive grafts for transplantation in HCV negative liver recipients have been reported. [29]

Recent publication from Cotter, et al have suggested the usage of Hepatitis C viremic organs among patients with and without Hepatitis C, after reviewing Scientific Registry of Transplant Recipients database. They reported 87 HCV RNA positive donor being used among Hepatitis C negative recipients, with 2-year graft survival being similar in all groups. [30]

In order to prevent complications in the graft, i.e. fibrosing cholestatic hepatitis, initiation of DAA should be considered as soon as possible in post LT phase. In the United States, approval of DAA by

insurance companies may be time consuming, but treatment is usually started within 4 weeks of transplant.

4. Conclusion

Though there has been a shift towards transplanting HCV viremic organs, there is still a need for long term data before a final consensus is reached. As per literature it seems that for now HCV NAT positive LT should be considered in a subset of patients such as those with acute liver failure in whom the timing of LT is sensitive, patients with hepatocellular carcinoma where there is a chance of dropout and patients with low MELD but with serious complications from portal hypertension, where their native MELD does not reflect the degree of their illness. Whether preemptive treatment with DAA after LT is sufficient or DAA treatment at the time of transplant would lead to better outcomes, remains to be determined.

Author Contributions

Haris Muhammad: Literature search, writing of the manuscript, final editing.
Muhammad Baraa Hammami: Editing, Literature search.
Peng-Sheng Ting: Critical review.
Cem Simsek: Critical Review, editing.
Behnam Saberi: Critical Review.
Ahmet Gurakar: Supervision, final editing.

Funding

None.

Competing Interests

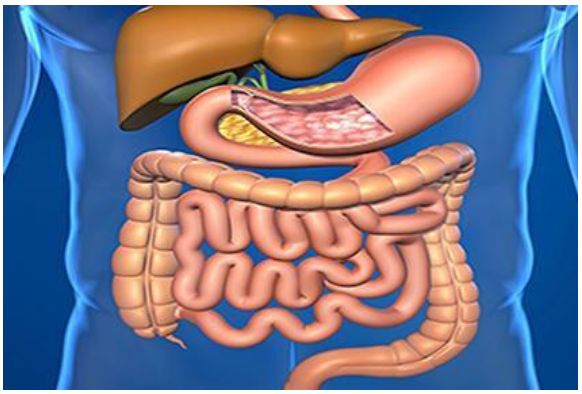
The authors authors have declared that no competing interests exist.

References

1. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. 2013; 57: 2164-2170.
2. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: Liver. Am J Transplant. 2018; 18: 172-253
3. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA. 2012; 308: 370-378.
4. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308: 2584-2593

5. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: A systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl. 2010; 16: 1228-1235
6. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. N Engl J Med. 2013; 368: 1907-1917
7. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS**.** Oral direct-acting agent therapy for hepatitis c virus infection. Ann Intern Med. 2017; 166: 637-648.
8. Carrión JA, Navasa M, García-Retortillo M, García-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: A randomized controlled study. Gastroenterology. 2007; 132: 1746-1756.
9. Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant. 2008; 8: 679-687.
10. Crespo G, Marino Z, Navasa M, Forns X. Viral hepatitis in liver transplantation. Gastroenterology. 2012; 142: 1373-1383. e1.
11. Manzardo C, Londoño MC, Castells L, Testillano M, Luis Montero J, Peñafiel J, et al. Direct-acting antivirals are effective and safe in HCV/HIV-coinfected liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study. Am J Transplant. 2018; 18: 2513-2522.
12. Rudd RA, Seth P, David F, Scholl L. Increase in drug and opioid-involved overdose deaths-United States, 2010-2015. Morb Mortal Wkly Rep. 2016; 65: 1445-1452.
13. Gladden RM, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths-27 states, 2013-2014. Morb Mortal Wkly Rep. 2016; 65: 837-843. doi: 10.15585/mmwr.mm6533a2
14. Goldberg DS, Blumberg E, McCauley M, Abt P, Levine M. Improving Organ utilization to help overcome the tragedies of the opioid epidemic. Am J Transplant. 2016; 16: 2836-2841.
15. Werbel WA, Durand CM. Pro: Use of hepatitis C virus-positive donors should be considered standard of care. Clin Liver Dis (Hoboken). 2018; 12: 100-104
16. Durand CM, Bowring MG, Thomas AG, Kucirka LM, Massie AB, et al. The drug overdose epidemic and deceased-donor transplantation in the United States: A national registry study. Ann Intern Med. 2018; 168: 702-711.
17. Bari K, Luckett K, Kaiser T, Diwan T, Cuffy M, et al. Hepatitis C transmission from seropositive, nonviremic donors to non-hepatitis C liver transplant recipients. Hepatology. 2018; 67: 1673-1682.
18. Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transplant. 2008; 14 Suppl 2: S36-44. doi: 10.1002/lt.21646.
19. Raziorrouh B, Jung MC, Schirren CA, Loehe F, Thiel M, Nitschko H, et al Antiviral therapy for recurrent hepatitis C after liver transplantation: sustained virologic response is related to genotype 2/3 and response at week 12. Eur J Gastroenterol Hepatol. 2008; 20: 778-783.

20. Saigal S, Choudhary NS, Saraf N, Gautam D, Lipi L, Rastogi A, et al Genotype 3 and higher low-density lipoprotein levels are predictors of good response to treatment of recurrent hepatitis C following living donor liver transplantation. Indian J Gastroenterol. 2015; 34: 305-309.
21. Ciesek S, Proske V, Otto B, Pischke S, Costa R, Lüthgehetmann M et al. Efficacy and safety of sofosbuvir/ledipasvir for the treatment of patients with hepatitis C virus re-infection after liver transplantation. Transpl Infect Dis. 2016; 18: 326-332.
22. Gonzalez SA, Trotter JF, et al. The rise of the opioid epidemic and hepatitis C-positive organs: A new era in liver transplantation. Hepatology. 2018; 67: 1600-1608.
23. Kling CE, Perkins JD, Landis CS, Limaye AP, Sibulesky L**.** Utilization of organs from donors according to hepatitis C antibody and nucleic acid testing status: Time for change. Am J Transplant. 2017; 17: 2863-2868
24. Northup PG, Argo CK, Nguyen DT, McBride MA, Kumer SC, Schmitt TM, et al. Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: A US National Transplant Registry analysis. Transpl Int. 2010; 23: 1038-1044.
25. Ting PS, Hamilton JP, Gurakar A, Urrunaga NH, Ma M, Glorioso J, et al. Hepatitis C-positive donor liver transplantation for hepatitis C seronegative recipients. Transpl Infect Dis. 2019; 21: e13194.
26. Wijarnpreecha K, Aqel BA, Pungpapong S, Taner B, Reddy KS, Leise MD, et al. Multicenter experience evaluating outcomes of HCV seropositive Donors to HCV-Seronegative [abstract]. Am J Transplant. 2019; 19 (suppl 3).
27. Chhatwal J, Samur S, Bethea ED, Ayer T, Kanwal F, Hur C, et al. Transplanting hepatitis C virus-positive livers into hepatitis C virus-negative patients with preemptive antiviral treatment: A modeling study. Hepatology. 2018; 67: 2085-2095.
28. Bethea ED, Samur S, Kanwal F, Ayer T, Hur C, et al. Cost Effectiveness of transplanting HCV-infected livers in to uninfected recipients with preemptive antiviral therapy. Clin Gastroenterol Hepatol. 2019; 17: 739-747.e8
29. Mazur RD, Goldberg DS. Temporal changes and regional variation in acceptance of Hepatitis C virus-viremic livers. Liver Transpl. 2019; 25: 1800-1810.
30. Cotter TG, Paul S, Sandıkçı B, Couri T, Bodzin AS, Little EC, et al. Increasing utilization and excellent initial outcomes following liver transplant of Hepatitis C Virus (HCV)-viremic donors into HCV-negative recipients: Outcomes following liver transplant of HCV-viremic donors. Hepatology. 2019; 69: 2381-2395



Enjoy *OBM Hepatology and Gastroenterology* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/hg