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Hepatitis C Virus Infection among Hematopoietic Cell Transplant Donors and Recipients: American Society for Blood and Marrow Transplantation Task Force Recommendations

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INTRODUCTION

In recent years, management of hepatitis C virus (HCV) infection has changed dramatically because of the approval of new antiviral therapies. The purpose of the American Society for Blood and Marrow Transplantation (ASBMT) Task Force on HCV infection in hematopoietic cell transplant (HCT) recipients is to provide guidance regarding diagnosis and management of HCV infection in donors and recipients of hematopoietic cells.

Limited data are available on treating HCV infection in HCT recipients. A group of experts in infectious diseases, hepatology, and HCT worked together to compile this document with 2 goals: to summarize the currently available data in the field and to provide evidence-based and expert opinion recommendations regarding early identification and treatment of HCV-infected donors and recipients to minimize barriers to HCT and improve care and outcomes in this population. In preparing this report, the committee recognizes that in the absence of data in donors and recipients of hematopoietic cells, clinicians would benefit from

preliminary guidance while awaiting the completion of appropriate studies.

The recommendations herein are based on synthesis of limited evidence, theoretical rationales, practical considerations, and author opinion. When appropriate, the level of the evidence and the strength of the recommendation have been rated by applying the system used for the Hepatitis C Guidance of the American Association for the Study of Liver Disease (AASLD) and Infectious Disease Society of American (IDSA) (<http://hcvguidelines.org>) (Table 1) [1]. However, for some individual recommendations, the level of the supporting evidence and strength of the recommendation could not be rated.

For this report, HCT is defined as transplant of any blood- or marrow-derived hematopoietic progenitor cells, regardless of whether the transplant is allogeneic or autologous and regardless of the cell source (ie, bone marrow, peripheral blood, or umbilical cord blood). The recommendations in this document are based on data from the following sources: research published in the peer-reviewed literature or presented at major national and international scientific conferences, safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or from manufacturers, drug interaction data, and prescribing information for FDA-approved products. Literature searches were conducted using medical subject

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Table 1
Grading System used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	Description
Level A*	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B*	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) that represents the level of the evidence that supports the recommendation and a letter (A, B, or C) that represents the strength of the recommendation.

* In some situations, such as for IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The FDA has suggested alternative study designs, including historical control subject or immediate versus deferred, placebo-controlled trials. For additional examples and definitions see the FDA link (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf>). In those instances for which there was a single predetermined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B. Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2011); (Shiffman, 2003)

headings and free text terms combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases; search terms included “HCV and Bone Marrow Cell Transplantation” and “HCV and Hematopoietic Stem Cell Transplantation.” Only articles published in English from 1990 to the present were considered for inclusion. The ASBMT plans to review these recommendations and update them to include advances in the published evidence.

EXECUTIVE SUMMARY

For more than a decade the mainstay of treatment for HCV infection was a combination regimen of pegylated IFN and ribavirin, but this regimen was associated with a poor rate of sustained virologic response (SVR) and poor tolerability, especially in cancer patients and HCT recipients [2,3]. Furthermore, almost 30% of infected HCT recipients could not be treated with pegylated IFN and ribavirin because of contraindications to the treatment combination [3]. The management of HCV infection in the general population has recently changed as a result of FDA approval of several direct-acting antiviral agents (DAAs), which have rendered IFN-containing regimens obsolete for almost all HCV genotypes.

This report, developed by the ASBMT, is specifically devoted to diagnosis and management of HCV infection in donors and HCT candidates and recipients. There are few data that answer important clinical questions for such donors or recipients. The online document from the AASLD-IDSAs, “Recommendations for Testing, Managing, and Treating Hepatitis C” (<http://www.hcvguidelines.org>), which is updated regularly throughout the year, was used as a resource in the development of this report but had no specific recommendations for these populations. Thus, this document was developed to provide expert opinion for clinicians who must make management decisions while awaiting adequately powered trials dealing with donors and HCT recipients.

Evidence is summarized, and, where possible, recommendations are provided. This report replaces the 2009

ASBMT-IDSAs guideline [4]. Several topics are new or expanded from that document (Table 2).

NATURAL HISTORY OF HCV INFECTION IN HCT RECIPIENTS: GEORGE B. MCDONALD AND MARCOS DE LIMA

Recommendations

- In all HCT survivors with active HCV infection, cofactors that can lead to fibrosis should be addressed. Patients should be counseled to avoid excessive weight gain, ethanol and medications or herbal supplements that are hepatotoxic, treatment of other causes of liver disease (nonalcoholic fatty liver disease, hepatitis B virus, HIV, and extrahepatic obstruction) (class I, level C), and mobilization of excess iron (class II, level C).
- All HCV-infected long-term HCT survivors should be evaluated for progression of liver disease every 6 to 12 months with a hepatic function panel, complete blood cell count, and evaluation of prothrombin time/international normalized ratio (class I, level C). If fibrosis is suspected in long-term HCT survivors, noninvasive tests such as serologic panels and transient elastography can be used to evaluate for the presence of advanced fibrosis (Scoring System for Histological Stage Metavir score \geq F3) and cirrhosis (Metavir score F4).
- HCV-infected HCT recipients should be vaccinated against hepatitis A virus and hepatitis B virus following HCT immunization protocols [4].
- Donors and HCT candidates with HCV infection should be counseled to use appropriate precautions to prevent transmission of HCV to others (class I, level C).
- For HCV-infected HCT long-term survivors with advanced fibrosis (Metavir score \geq F3), surveillance for hepatocellular carcinoma (HCC) with ultrasonography every 6 months is recommended (class I, level C). For patients with cirrhosis, endoscopic surveillance for esophageal varices is recommended (class I, level A).
- HCT recipients who develop end-stage liver disease can be considered for liver transplant; in rare cases, a living

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321**Table 2**
Summary of Changes Compared with the Guidelines Published in 2009 [4]

Major Change	Starting Page
Updated background on natural history of HCV infection in HCT recipients	7
New recommendations regarding HCV screening:	
1. Screening of all hematopoietic cell donors within 30 days before cell harvest with FDA-approved HCV antibody and RNA testing in accordance with the FACT standards and FDA guidance (class I, level C)	11
2. Screening of all long-term survivors of HCT, especially those with epidemiologic risk factors including those transplanted in the era before routine donor and blood product screening (class I, level C)	
Updated background on impact of HCV infection on eligibility to donate hematopoietic cells or undergo HCT	14 (Table 3)
New section regarding monitoring HCV in chronically infected HCT recipients:	
1. ALT level should be evaluated at entry into care, 2 to 8 weeks after completion of the conditioning regimen, every 2 to 8 weeks during maintenance chemotherapy or immunosuppressive treatment, and every 3 to 6 months thereafter (class II, level C)	17
2. In HCT recipients with chronic HCV infection, routine monitoring of HCV RNA is not recommended. However, viral load should be considered for patients who have an unexplained elevation of ALT (class II, level C). HCV RNA should be measured in all patients at entry into care, and monitoring of viral load should be performed in patients receiving HCV treatment according to the AASLD-IDS A HCV guidance (http://www.hcvguidelines.org/) (class I, level C).	
New section regarding fibrosis assessment in HCV-infected HCT candidates and recipients using serologic markers and ultrasound-based VCTE	20
New recommendations regarding antiviral therapy for donors and HCT candidates and recipients:	
1. Timing of antiviral therapy	24
2. Treatment interruption is not recommended (class I, level C)	24
3. IFN-based regimens should be avoided because of their suboptimal efficacy and safety (class I, level B)	25
4. DAA combinations of potential use in HCV-infected HCT recipients extrapolated from studies in other patient populations	28
New section and table on drug–drug interactions in HCV-infected HCT candidates and recipients receiving DAAs and conditioning regimens or immunosuppressive agents	31 Table 4

donor liver transplant from the original hematopoietic cell donor may be feasible (class I, level C).

Evidence Summary

Course of HCV infection to 1 year after HCT

HCV infection has hepatic and extrahepatic manifestations. Hepatic manifestations in HCT recipients in addition to those seen in immunologically normal hosts include (1) an increased risk of fatal sinusoidal obstruction syndrome (previously known as veno-occlusive disease) among patients with chronic HCV infection who receive sinusoidal endothelial cell toxins (eg, cyclophosphamide, etoposide, melphalan, thiopeta, total body irradiation ≥ 12 Gy) as part of the conditioning therapy [5]; (2) hepatic inflammation occurring 3 to 6 months after HCT, coincident with immune reconstitution and discontinuation of immunosuppressive drugs [5]; (3) liver decompensation among patients who had cirrhosis at the time of transplant [6,7]; and (4) rarely, fatal fibrosing cholestatic hepatitis C before day 100 in patients receiving mycophenolate mofetil [8]. Fibrosing cholestatic hepatitis is an aggressive form of viral hepatitis caused by either hepatitis B virus or HCV that causes rapid clinical deterioration, characterized histologically by extensive fibroblastic portal-to-portal bridging, ductular proliferation, cholestasis, high intrahepatocyte viral load, and inflammation [8].

Extrahepatic manifestations of HCV infection after HCT have been suggested by epidemiologic studies and include greater 1- to 2-year nonrelapse-related mortality than in HCV-negative control subjects, including an excess of deaths related to bacterial infections [6,7]. It is not clear if the higher mortality is due to HCV per se, the presence of undetected hepatic fibrosis and portal hypertension, or chronic viral coinfections (such as hepatitis B virus infection or HIV infection) at the time of transplant.

Course of HCV infection between 1 and 10 years after HCT

Coincident with immune reconstitution after HCT, serum alanine aminotransferase (ALT) levels wax and wane in most HCV-infected patients. The course of this chronic hepatitis is

usually uncomplicated for 10 years after HCT, but, rarely, patients may progress to cirrhosis. Serum aminotransferase elevations can be seen in 57% of HCV-infected patients between 5 and 10 years after HCT [5]. In several series no excess mortality was noted in HCV-infected patients up to 10 years after HCT [5,9,10]. In some patients, however, the duration of HCV infection before HCT can only be estimated, and the extent of fibrosis is unknown at the time of HCT; such patients may experience progressive liver disease that only becomes apparent after HCT [6,7].

Course of HCV infection 10 to 40 years after HCT

Chronic HCV is the leading cause of cirrhosis after HCT, and the time to cirrhosis is shorter in patients with chronic HCV infection who undergo HCT than in patients with chronic HCV infection who do not undergo HCT [11,12]. About one third of HCV-infected 40-year survivors of HCT develop end-stage liver disease (cirrhosis, HCC, or disease requiring liver transplant). HCT recipients who develop end-stage liver disease can be considered for liver transplant; living donor liver transplant from the original hematopoietic cell donor has been described [13,14].

Knowledge Gaps

- What is the natural history of HCV in HCT in the era of current immunosuppressive regimens?
- What are the predictors of liver disease progression in HCT recipients?
- Do effective antiviral drugs alter the course of HCV-related fibrosing cholestatic hepatitis, hepatic fibrosis, and cirrhosis in HCV-infected survivors of HCT?

HCV SCREENING IN DONORS OF HEMATOPOIETIC STEM CELLS, HCT CANDIDATES, AND LONG-TERM SURVIVORS: SARAH P. HAMMOND AND JOHN R. WINGARD

Recommendations

- All hematopoietic cell donors should be screened for HCV within 30 days before cell harvest with FDA-approved HCV antibody (anti-HCV) and RNA testing in

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accordance with the Foundation for the Accreditation of Cellular Therapies (FACT) standards and FDA guidance (class I, level C).

- All HCT candidates should be screened for HCV with FDA-approved anti-HCV testing (class I, level C).
- All long-term survivors of HCT should be screened for HCV infection based on the current recommendations for screening in non-HCT recipients, with special attention to those with epidemiologic risk factors, including those transplanted in the era before routine donor and blood product screening (class I, level C).

Evidence Summary

In the general US population, risk-based screening for HCV infection with anti-HCV testing (with reflex HCV RNA testing for individuals with positive results) is recommended by the Centers for Disease Control and Prevention [15], US Preventive Services Task Force [16], and AASLD, IDSA, and International Antiviral Society–USA [1]. Individuals considered at high risk include not only intravenous drug users but also individuals born between 1945 and 1965 [15].

Transmission of HCV from HCV-infected bone marrow donors to uninfected recipients was first documented in the early 1990s [17]. FACT has issued standards for US centers performing HCT that include HCV screening of allogeneic donors within 30 days before stem cell harvest using tests required by applicable laws and regulations [18]. The FDA has issued guidelines recommending that such donors be screened with FDA-licensed antibody and nucleic acid tests [19]. A positive test result for anti-HCV (using third-generation tests) in the setting of undetectable serum HCV RNA indicates past infection (resolved spontaneously or therapeutically), acute HCV infection during a period of low-level viremia, or a false-positive test result [1,20].

False-positive anti-HCV tests are more common with earlier generation testing, especially if confirmation with the recombinant immunoblot assay was not included in the method. In such a case the HCV-treating providers should retest the donor for anti-HCV and HCV RNA to exclude the presence of active infection and seek guidance from an infectious disease or hepatology expert.

The presence of serum HCV RNA indicates current and active infection. If the viremia persists for more than 6 months postexposure, the infection is considered chronic and is not likely to resolve spontaneously.

FACT and FDA guidance on HCT donor screening does not extend to HCT candidates and recipients. Overall, HCV screening in HCT candidates establishes a pretransplant baseline and identifies patients who might benefit from HCV treatment after transplant. There is usually insufficient time to complete a course of HCV therapy before HCT. Chronic HCV can be associated with false-negative anti-HCV test results in immunosuppressed patients [20], including HCT recipients [21]. Such patients have a positive serum HCV PCR test.

In a prospective study in allogeneic HCT recipients from 15 European transplant centers, data on pretransplant HCV RNA were available for 182 patients, and 11 were found to have viremia, including 6 anti-HCV–negative patients [21]. In HCT candidates and recipients, screening with HCV RNA testing in addition to anti-HCV serologic testing is advocated by many experts (class IIb, level C). In 1 study, 13% of HCV-infected patients with a positive anti-HCV test result before HCT had a negative anti-HCV test result after HCT [22].

Knowledge Gap

- How frequently are HCT candidates or HCV recipients seronegative for HCV with third-generation tests despite serum nucleic acid evidence of active infection?
- What is the most cost-effective algorithm for screening HCT candidates and recipients?

IMPACT OF HCV INFECTION ON ELIGIBILITY TO DONATE HEMATOPOIETIC STEM CELLS OR UNDERGO HCT:

HARRYS A. TORRES AND JOHN R. WINGARD

Recommendations

- HCV infection in donors or potential HCT recipients should not be an absolute contraindication for HCT (class I, level C) (Table 3).
- The risk of HCV transmission is extremely low when seronegative and HCV RNA–negative HCT candidates receive HCT from donors of hematopoietic stem cells with positive anti-HCV and undetectable HCV RNA (class I, level C).
- HCV-infected donors should be assessed for advanced chronic liver disease and other extrahepatic manifestations of HCV to recommend an optimal management of their disease (class I, level C).
- HCV-infected donors should be screened for other coinfections (eg, HIV). HIV–HCV–coinfecting individuals should not be considered as donors for HIV-seronegative recipients, according to standard HCT guidelines [4].
- HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV provided the recipient has full understanding of the potential consequences given the viral characteristics of the donors' HCV infections (class IIa, level C).
- If the donor is HCV RNA positive and transplantation to an HCV-infected or -uninfected recipient is considered, the donor should start antiviral therapy immediately with the goal of reducing the infectious potential of the donor, ideally attaining undetectable plasma HCV RNA in the donor before stem cell harvest (class I, level C).
- Selection of HCV-infected candidates for HCT should be based on the extent of liver fibrosis and degree of portal hypertension (class I, level C).

Evidence Summary

Donors with positive HCV screening test results

As recommended for the general population [1], donors (or HCT recipients) found to have positive results for anti-HCV and negative results for HCV RNA by PCR using an FDA-approved sensitive HCV RNA test should be informed they do not have evidence of current (active) HCV infection. Repeat HCV RNA testing at a later date (eg, 1 to 2 months) is typically unnecessary but can be performed when there is strong suspicion of acute infection or in patients with ongoing risk factors for HCV infection [1].

Up to 100% of infected donors transmit HCV to uninfected HCT recipients [17]. If no alternative donor is available and if time does not permit treatment of the infected donor to eliminate HCV from the infusion product, the use of HCV-infected hematopoietic cells for an HCV-uninfected recipient is not contraindicated. New DAAs could potentially provide a virologic cure after HCT in most patients and may

Table 3
Eligibility to Donate Hematopoietic Stem Cells or Undergo HCT according to Different Clinical Scenarios

Clinical Scenario	Donor Anti-HCV	Donor HCV RNA	HCT Candidate/Recipient Anti-HCV	HCT Candidate/Recipient HCV RNA	Recommendation for Donor	Recommendation for HCT Candidate/Recipient
1	Negative	Negative	Negative	Negative	Proceed with stem cell harvest.	Proceed with HCT.
2	Negative	Positive	Negative	Negative	Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.*	Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance. [†]
3	Negative	Positive	Positive	Negative	Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.*	Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance. [†]
4	Negative	Positive	Positive	Positive	Proceed with stem cell harvest. [‡]	Proceed with HCT. [‡] Start antiviral therapy, when possible. [§]
5	Negative	Positive	Negative	Positive	Proceed with stem cell harvest. [‡]	Proceed with HCT. [‡] Start antiviral therapy, when possible. [§]
6	Negative	Negative	Positive	Negative	Proceed with stem cell harvest.	Proceed with HCT.
7	Negative	Negative	Positive	Positive	Proceed with stem cell harvest.	Proceed with HCT. Start antivirals, when possible. [§]
8	Negative	Negative	Negative	Positive	Proceed with stem cell harvest.	Proceed with HCT. Start antivirals, when possible. [§]
9	Positive	Negative	Negative	Negative	Proceed with stem cell harvest.	Proceed with HCT.
10	Positive	Positive	Negative	Negative	Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.*	Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance. [†]
11	Positive	Positive	Positive	Negative	Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.*	Proceed with HCT. [†] Monitor HCV RNA managing acute infection per HCV guidance. [†]
12	Positive	Positive	Negative	Positive	Proceed with stem cell harvest. [‡] Manage infection per HCV guidance.	Proceed with HCT. [‡] Start antivirals, when possible. [§]
13	Positive	Positive	Positive	Positive	Proceed with stem cell harvest. [‡] Manage infection per HCV guidance.	Proceed with HCT. [‡] Start antivirals, when possible. [§]
14	Positive	Negative	Positive	Positive	Proceed with stem cell harvest.	Proceed with HCT. Start antivirals, when possible. [§]
15	Positive	Negative	Negative	Positive	Proceed with stem cell harvest.	Proceed with HCT. Start antivirals, when possible. ^{‡,§}
16	Positive	Negative	Positive	Negative	Proceed with stem cell harvest.	Proceed with HCT.

* When possible, start antiviral therapy immediately, attaining viral clearance before stem cell harvest to reduce the risk of HCV transmission. If HCT must be done urgently, stem cell harvest from a viremic donor should be considered.

[†] Per HCV guidance, monitor HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months after the time of infection to determine spontaneous viral clearance versus active HCV. Detectable HCV RNA at 6 months after onset of infection will identify most persons who need HCV therapy (<http://hcvguidelines.org/full-report/management-acute-hcv-infection>).

[‡] HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV (see text for details).

[§] HCV-infected HCT candidates should be started on therapy and should complete HCV therapy before transplant, when possible.

^{||} HCT donors and candidates with positive anti-HCV in the setting of undetectable HCV RNA should have repeat HCV RNA testing when there is strong suspicion of acute infection or in patients with ongoing risk factors for HCV infection (see text for details).

halt liver disease progression in HCT survivors. The risk of dying from the underlying hematologic malignancy without the transplant outweighs the risk of acquiring potentially curable HCV. However, the donor should be assessed for advanced chronic liver disease per current HCV guidance [1] as well as extrahepatic manifestations of HCV (eg, lymphoproliferative diseases) and coinfections (eg, HIV) that might contraindicate donation (class I, level C) [4].

The risk of transmission of HCV was decreased to nearly 0 if HCV RNA was undetectable at the time of hematopoietic cell donation [17]. In viremic donors, viral clearance with DAAs before cell harvest may be attempted if feasible to reduce the risk of HCV transmission, because most donors will attain undetectable HCV PCR within 4 weeks of starting currently available DAAs [4,23,24]. The timing of HCV therapy is further discussed below (see When to Treat HCV Infection in Donors and Autologous or Allogeneic HCT Candidates and Recipients).

HCT candidates with positive HCV screening test results

Similar to what is recommended for donors, HCT candidates with positive test results for anti-HCV in the setting of undetectable HCV RNA should be evaluated to exclude acute infection by repeating HCV RNA. HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV, provided the recipient has full understanding of the potential consequences (class IIa, level C) [5]. The potential consequences include infections with different genotypes (eg, genotype 3) or resistance-associated variants (such as NS5A variants) potentially associated with a higher rate of virologic failure. Treatment recommendations in HCT candidates are further discussed below (see When to Treat HCV Infection in Donors and Autologous or Allogeneic HCT Candidates and Recipients). All individuals (donors and recipients) with HCV infection should be referred to a practitioner able to provide comprehensive management of HCV [1].

Knowledge Gaps

- Studies are needed to determine the magnitude of risk for HCV transmission when HCV-infected donors have achieved undetectable HCV RNA but have not completed their recommended treatment course.

MONITORING HCV IN HCT RECIPIENTS WITH CHRONIC HCV INFECTION: HARRYS A. TORRES AND MARCOS DE LIMA

Recommendations

- In HCT recipients with chronic HCV infection, ALT level should be evaluated at entry into care, 2 to 8 weeks after completion of the conditioning regimen, every 2 to 8 weeks during maintenance chemotherapy or immunosuppressive treatment, and every 3 to 6 months thereafter (class II, level C).
- In HCT recipients with chronic HCV infection, routine monitoring of HCV RNA is not recommended. However, viral load should be considered for patients who have an unexplained elevation of ALT (class II, level C). HCV RNA should be measured in all patients at entry into care, and monitoring of viral load should be performed in patients receiving HCV treatment according to the

AASLD-IDSA HCV guidance (<http://www.hcvguidelines.org/>) (class I, level C).

Evidence Summary

Acute exacerbation of chronic HCV infection, indicated by a significant elevation of serum aminotransferase levels over the baseline level in the absence of other potential causes of acute hepatitis, can occur in both immunocompetent [25] and immunocompromised cancer patients [26]. However, there are no standard definitions for this phenomenon. In a retrospective study of 308 patients with cancer and chronic HCV infection, 11% were identified as having acute exacerbation of chronic HCV infection, defined as a 3-fold or greater increase in serum ALT level from baseline in the absence of (1) infiltration of the liver by cancer, (2) use of hepatotoxic medications, (3) blood transfusion within 1 month of elevation of ALT level, or (4) other systemic infections affecting the liver (including hepatitis A virus, hepatitis B virus, cytomegalovirus, adenovirus, herpes simplex virus, varicella-zoster virus, and HIV infections) [26]. In that study, acute exacerbation (significant ALT elevation) of HCV infection during chemotherapy prompted clinicians to discontinue chemotherapy in nearly half of affected patients [26].

Enhanced HCV replication (also known as HCV reactivation [26]) has been defined as an increase in HCV RNA viral load of at least 1 log₁₀ IU/mL over baseline after chemotherapy or immunosuppressive therapy [26] because chronically infected patients have stable HCV RNA levels that may vary by approximately .5 log₁₀ IU/mL [27]. The increased replication of HCV appears to be associated with a more indolent course than hepatitis B virus reactivation [28]; only a few reports of deaths have been associated with increased HCV replication [8,29]. Regrettably, the published data on simultaneous changes in ALT levels and HCV viral load are limited and not sufficient for examination of whether a correlation exists between enhanced viral replication and hepatocellular injury [26], as has been described for patients with chemotherapy-induced hepatitis B virus reactivation.

Little is known about acute exacerbation of HCV infection in HCT recipients, with emerging data after autologous and allogeneic HCT recently presented [22,30]. However, such studies should be considered preliminary because most were retrospective analyses of small numbers of patients. In 1 prospective study, aspartate aminotransferase (AST) levels were compared between HCV-infected and HCV-negative HCT recipients [5]. A severe acute flare of hepatitis (AST >10 times the upper limit of normal) developed in 11 of 36 HCV-infected patients (31%) who survived at least 1 year after HCT but only 6 of 115 HCV-negative patients (5%) ($P < .0001$). Data on HCV RNA were not presented; thus, it was not possible to determine whether the increase in AST level in patients receiving chemotherapy resulted from coinfections, drugs, or enhanced HCV replication in the setting of immunosuppression.

Patients with significant ALT elevations (eg, ≥ 3 -fold increase from the upper limit of normal) should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury. HCV-treating physicians should participate in the diagnostic workup of acute exacerbation of HCV to exclude other potential explanations for ALT increase (eg, infiltration of the liver by cancer, hepatotoxic medications, blood transfusion within 1 month, the hepatic presentation of liver graft-versus-host disease [GVHD], or other systemic infections affecting the liver).

777 Knowledge Gaps

- 778
- 779 • Prospective studies are needed to determine the inci-
- 780 dence, clinical implications, and outcome of acute
- 781 exacerbation of chronic HCV infection in HCT
- 782 recipients.
- 783 • What is the best strategy for monitoring HCV infection
- 784 around the time of HCT?

786 FIBROSIS ASSESSMENT IN HCV-INFECTED HCT

787 CANDIDATES AND RECIPIENTS: MAYA GAMBARIN-

788 GELWAN AND MARK S. FRIEDMAN

789 Recommendations

- 790 • All HCV-infected HCT candidates should undergo
- 791 assessment of the stage of liver fibrosis and the pres-
- 792 ence of cirrhosis (class I, level C).
- 793 • The presence of cirrhosis may affect duration and type
- 794 of HCV therapy and will identify patients who need to
- 795 be screened for HCC and the presence of esophageal
- 796 varices (class I, level C).
- 797 • The decision to perform a liver biopsy should be made
- 798 only after careful consideration of the risks and benefits
- 799 of the procedure (class I, level B).
- 800 • Serologic marker panels for detection of fibrosis have
- 801 not been studied in HCV-infected HCT candidates, and
- 802 their use is not recommended (class IIb, level C).
- 803 • Ultrasound-based vibration-controlled transient elas-
- 804 tography (FibroScan VCTE; Echosens) has not been
- 805 Q6 studied in HCT recipients, and thus results should be
- 806 interpreted with caution (class II, level C).

809 Evidence Summary

810 All HCV-infected HCT candidates should undergo assess-
811 ment of the stage of liver fibrosis and the presence of
812 cirrhosis (class I, level C). The presence of advanced fibrosis
813 (Metavir \geq F3) or cirrhosis (Metavir F4) may have a signifi-
814 cant impact on HCT eligibility, the choice of conditioning
815 regimen, HCV therapy, and risk of HCC.

817 Liver biopsy

818 Liver biopsy has been the criterion standard for histo-
819 pathologic assessment of fibrosis in patients with chronic
820 HCV infection, particularly when the stage of fibrosis and
821 presence or absence of cirrhosis may guide subsequent
822 management. However, liver biopsy is an imperfect criterion
823 standard because it is associated with sampling limitations
824 and error, is invasive, and carries a risk of complications.
825 Individuals with hematologic malignancies requiring HCT
826 may be at particular risk for complications [31] and often
827 require a transjugular approach because of severe throm-
828 bocytopenia [32]. The decision to perform a liver biopsy
829 should be made only after careful consideration of the risks
830 and benefits of the procedure (class I, level B) [33].

833 Serologic marker panels for detection of fibrosis

834 Tests for serologic markers of fibrosis have become widely
835 available in the past several years and are used extensively in
836 patients with chronic HCV infection. The AST-to-platelets
837 Q7 ratio and FIB-4 are easy to calculate using data available on
838 routine laboratory testing. Four commercial serum marker
839 panels have been validated in the general population of pa-
840 tients with chronic HCV infection: FibroTest/FibroSure
841 Q8 (LabCorp), Hepascore (Quest Diagnostics), FibroSpect

(Prometheus Corp), and the European Liver Fibrosis Study
842 Group panel (not available in the United States). No panel has
843 yet emerged as standard of care or is FDA approved; how-
844 ever, all 4 panels have demonstrated accuracy in distin-
845 guishing patients with significant fibrosis (Metavir score
846 F2 to F4) from those without significant fibrosis (Metavir
847 score F0 or F1) [34]. Because individual markers in these
848 panels include aminotransferases, platelets, coagulation pa-
849 rameters, γ -glutamyl transferase, total bilirubin, haptog-
850 globin, gamma globulins, and so on, the results might be
851 unreliable in HCT candidates and recipients because of
852 cytopenias, ongoing systemic inflammation, drug-related
853 liver damage, and infection. These panels have not been
854 studied in candidates for HCT or in HCT recipients, and their
855 use is not recommended in either population.

857 Vibration-controlled transient elastography

858 Ultrasound-based elastography in the form of FibroScan
859 VCTE was approved by the FDA in April 2013. This procedure
860 has been endorsed by the AASLD “to be used by clinicians
861 providing care for patients with liver disease to evaluate liver
862 fibrosis at the point of care” [35]. VCTE is quick, is done at the
863 Q9 time of the clinic visit, is noninvasive, has good reproduc-
864 ibility, is relatively inexpensive, and provides information
865 about a large area of the liver. VCTE has been extensively
866 studied in patients with chronic HCV infection. In a recent US
867 multicenter study, VCTE demonstrated a positive predictive
868 value of 75.6% to 80.8% and a negative predictive value of
869 55.0% to 84.7% for diagnosis of significant fibrosis ($F \geq 2$) and
870 an estimated positive predictive value of 41.6% to 60.4% and
871 negative predictive value of 95.6% to 97.6% for diagnosis of
872 cirrhosis [36]. VCTE would plausibly be useful for assessment
873 of advanced fibrosis, particularly to rule out cirrhosis in HCT
874 candidates and recipients, although these patient pop-
875 ulations have not been extensively studied [37,38].

877 Knowledge Gaps

- 878 • Reliability of serologic markers of fibrosis and FibroScan
- 879 VCTE in predicting the presence of advanced fibrosis
- 880 and cirrhosis in HCT candidates and recipients.
- 881 • Effect of leukemic infiltration of hepatic sinusoids,
- 882 lymphoma of the liver, or extramedullary hematopoi-
- 883 esis with sinusoidal fibrosis on the accuracy of VCTE.
- 884 • Role of VCTE as a predictor of hepatotoxicity in HCT
- 885 recipients.

889 WHEN TO TREAT HCV INFECTION IN DONORS AND

890 AUTOLOGOUS OR ALLOGENEIC HCT CANDIDATES AND

891 HCT SURVIVORS: MAYA GAMBARIN-GELWAN, SERGIO

892 GIRALT, AND GEORGE B. MCDONALD

893 Recommendations

- 894 • HCV-infected donors should be evaluated for HCV
- 895 therapy and treated before cell harvest to prevent
- 896 transmission of HCV to uninfected recipients, if possible
- 897 (class I, level C).
- 898 • All HCT candidates with HCV infection should be eval-
- 899 uated for HCV therapy before the start of conditioning
- 900 therapy; after transplant, HCV-infected survivors
- 901 should also be evaluated for therapy (class I, level B).
- 902 • When possible, HCV-infected HCT candidates should be
- 903 started on therapy and should complete therapy for
- 904 HCV before transplant (class IIa, level C).
- 905
- 906

- After HCT, the following patients should be treated for HCV without delay: HCV-infected patients who develop fibrosing cholestatic hepatitis C, patients with cirrhosis whose condition is deteriorating, and patients who underwent HCT for HCV-related lymphoproliferative disorders (class I, level C).
- After HCT, treatment for HCV can be deferred until after immune reconstitution for patients not meeting the criteria above (class I, level C).
- All HCV-infected long-term survivors of HCT should be offered antiviral therapy (class I, level C).
- HCV therapy should be undertaken only with the intention of completion of the full course of therapy as defined in the AASLD-IDS A Hepatitis C Guidance (<http://www.hcvguidelines.org/>). Treatment interruption is not recommended (class I, level C).
- IFN-based regimens should be avoided in donors and HCT candidates/recipients with HCV infection because of their suboptimal efficacy and safety (class I, level B).
- HCV therapy should be undertaken by providers experienced in management of HCV in HCT recipients in close collaboration with transplant teams (class I, level B).

Evidence Summary

Treatment of HCV-infected donors before HCT

Several case reports have described successful prevention of HCV transmission through treatment of HCV-infected donors before cell harvest [5,24,39,40]. When there are oncologic imperatives for moving quickly to transplant, DAAs should be able to clear extrahepatic HCV from donors more quickly than IFN and ribavirin can without significant toxic effects on the donor marrow. Once initiated, a full course of antiviral therapy should be completed in donors based on the current treatment recommendations for individuals with HCV infection [1].

The risk of HCV transmission at various time points during HCV therapy has not been studied. Plausibly the risk of transmission should be sharply reduced if serum HCV RNA levels are below the level of detection for the assay.

Treatment of HCV-infected candidates before HCT and recipients after HCT

Data are lacking regarding treatment of HCV-infected HCT candidates. DAA therapy before HCT should be considered.

Prompt treatment of HCV infection after transplant is urgent for 3 groups: patients with fibrosing cholestatic HCV [8], patients with cirrhosis whose condition is deteriorating [41], and patients who underwent HCT for HCV-related lymphoproliferative disorders [22,42]. It is not known, however, whether the efficacy of DAA therapy is affected by dysfunctional immunity after therapy for cancer. It is also not known whether eliminating HCV before HCT improves the outcome of transplant by, for example, reducing the risks of post-HCT fatal sinusoidal obstruction syndrome, liver decompensation, fibrosing cholestatic hepatitis, or recurrent lymphoma [43,44]. Once HCV therapy is started in either HCT candidates or recipients, treatment interruption is not recommended, because it is associated with increased risk of treatment failure [2].

The alternative to pre-HCT therapy for HCV is to treat after HCT using DAAs after immune reconstitution [22]. Although published data are limited on outcomes of DAA therapy in HCT recipients, SVR rates of 70% to 96% have been

observed in patients who received DAAs during immunosuppressive therapy after liver transplant [43,44].

A preliminary observational study suggested that IFN-sparing regimens were well tolerated and effective in 10 HCT recipients and have potential to improve patient outcomes [22]. Combination DAA therapy appears to be safe and effective in HCV-infected allogeneic and autologous HCT recipients after a follow-up period of 6 months after transplant [22]. Some experts advocate waiting for 6 months after the transplant to allow tapering of immunosuppression agents and GVHD prophylaxis, which might result in higher SVR rates and reduction of drug–drug interactions.

Flare of GVHD that occurs after tapering immunosuppressive therapy could be confused for HCV exacerbation and/or medication toxicity in those receiving antivirals. Some clinicians may still choose to defer DAA therapy until immunosuppressive treatment has been discontinued to avoid drug–drug interactions.

IFN-based regimens should be avoided in donors and HCT candidates with HCV infection because of their suboptimal efficacy and safety (class I, level B). Data are not available regarding the impact of treatment regimens consisting of ribavirin plus DAA in HCV-infected HCT recipients.

Treatment of HCV-infected long-term HCT survivors

About one third of HCV-infected long-term HCT survivors develop end-stage liver disease or HCC [11,12]. Thus, all HCV-infected long-term HCT survivors should be offered DAA therapy. The rationale for universal treatment of infected survivors is that it can prevent transmission of HCV, delay the development of cirrhosis, and reduce long-term consequences of chronic HCV infection, including development of HCC, extrahepatic manifestations of HCV, and possible need for liver transplantation.

Knowledge Gaps

- Should all HCV-infected donors and HCT candidates be treated with antivirals before HCT?
- What is the optimal timing of antiviral therapy for HCT candidates?
- How effective and safe are DAAs given to HCT candidates or recipients?
- What is the effect of virologic cure of HCV on the risk of sinusoidal obstruction syndrome and other liver-related complications of HCT in HCV-infected individuals?
- Does antiviral therapy prevent post-HCT liver disease progression and relapse of HCV-associated non-Hodgkin lymphoma?
- Does recovery of a full immunologic repertoire after HCT affect the efficacy of antiviral treatment?

ROLE OF DAA COMBINATIONS IN HCV-INFECTED HCT RECIPIENTS: PEARLIE P. CHONG, MARK S. FRIEDMAN, AND HENRY MASUR

Recommendations

Recommendations by HCV genotype as of July 2015

- For infection with genotype 1a, 1b, or 4 HCV, treatment with 1 of the following 3 DAA combinations is recommended:
 - Daily fixed-dose combination of ledipasvir and sofosbuvir.

- 1037 ○ Twice-daily fixed-dose combination of ombitasvir,
1038 paritaprevir, ritonavir, and dasabuvir with or without
1039 ribavirin.
1040

- 1041 ○ Daily sofosbuvir plus simeprevir.
1042

1043 The choice of regimen should be individualized on the
1044 basis of patient-specific data, including potential drug
1045 interactions.
1046

- 1047
1048 • For infection with genotypes 2, 3, or 5 HCV, the
1049 preferred regimen is sofosbuvir plus weight-based
1050 ribavirin.
1051 • Monotherapy with a DAA is not recommended for any
1052 patient with HCV infection (class III, level A).
1053

1054 *Treatment considerations in specific patient populations*

- 1055
1056 • HCT recipients often receive multiple drugs that could
1057 have pharmacologic interactions with DAAs or toxic
1058 effects that overlap with those of DAAs. Treating phy-
1059 sicians should be mindful of potential drug interactions
1060 and/or side effects, although this has not been exten-
1061 sively studied in HCT recipients.
1062 • In patients with mild (creatinine clearance 60 to
1063 89 mL/min) to moderate (creatinine clearance 30 to
1064 59 mL/min) renal impairment, no dosage adjustment is
1065 required for sofosbuvir plus simeprevir, ledipasvir plus
1066 sofosbuvir, or ombitasvir, paritaprevir, ritonavir, and
1067 dasabuvir (class I, level A). The total daily dose of
1068 ribavirin should be reduced for patients with creatinine
1069 clearance ≤ 50 mL/min [45].
1070 • In patients with severe renal impairment (creatinine
1071 clearance 15 to 29 mL/min) or with end-stage renal
1072 disease, safety and efficacy data for DAAs are not
1073 available; treatment can be contemplated after
1074 consultation with an expert (class IIb, level C) or as new
1075 data in this patient population become available. If
1076 ribavirin used, dose should be reduced [45].
1077 • Patients coinfecting with HIV and HCV should be treated
1078 like HCV-monoinfected patients, except that in-
1079 teractions with antiretroviral medications must be
1080 recognized and managed (class I, level B).
1081

1082 *Evidence Summary*

1083 DAAs are oral agents that target various HCV-encoded
1084 proteins vital to the replication of the virus. When used in
1085 combination, DAAs are capable of curing HCV infection;
1086 DAAs have demonstrated excellent rates of SVR and favorable
1087 safety profiles in multiple phase III clinical trials [46–51].
1088

1089 Unfortunately, the efficacy and safety of DAAs in HCV-
1090 infected HCT recipients have not been extensively studied
1091 or documented. The recommendations above are extrapo-
1092 lated from studies in other patient populations. The optimal
1093 therapy for HCV is evolving rapidly and will continue to
1094 evolve as multiple new drugs are approved and as more
1095 studies are reported. The recommendations above should be
1096 compared with the online AASLD-IDS A Hepatitis C Guidance
1097 for the management of HCV infection, which are updated
1098 frequently as new data emerge (<http://www.hcvguidelines.org/news/hcv-guidance>).
1099

1100 The choice of DAA regimen and duration of DAA treat-
1101 ment for HCV-infected HCT recipients should be informed by

1102 prior treatment experience, HCV genotype, and the degree of
1103 fibrosis. The combination of sofosbuvir and daclatasvir is
1104 approved by the FDA for use in the United States in patients
1105 with genotype 3 HCV infection [52].
1106

1107 *Knowledge Gaps*

- 1108 • Efficacy and safety of various DAA regimens in HCT
1109 recipients.
1110 • Optimal duration of DAA regimens in HCT recipients.
1111

1112 **DRUG–DRUG INTERACTIONS IN HCV-INFECTED HCT 1113 CANDIDATES AND RECIPIENTS RECEIVING DAAS AND 1114 CONDITIONING REGIMENS OR IMMUNOSUPPRESSIVE 1115 AGENTS: PATRICK J. KIEL**

1116 *Recommendations*

- 1117
1118 • Physicians should frequently assess for drug–drug
1119 interactions in HCV-infected HCT recipients (class I,
1120 level C).
1121 • HCT candidates should not receive DAAs concomitantly
1122 with the chemotherapy preparative regimen if the
1123 potential for drug–drug interactions exists (class I,
1124 level C).
1125 • In patients receiving tacrolimus concomitantly with
1126 paritaprevir and ritonavir, increased therapeutic drug
1127 monitoring and a 50% to 75% decrease in the tacrolimus
1128 dose may be required (class IIb, level B).
1129 • In patients receiving cyclosporine concomitantly with
1130 paritaprevir and ritonavir, increased therapeutic drug
1131 monitoring and a 35% to 50% decrease in the cyclo-
1132 sporine dose may be required (class IIb, level B).
1133 Sofosbuvir should not be administered concomitantly
1134 with cyclosporine.
1135 • In patients receiving sirolimus concomitantly with
1136 paritaprevir and ritonavir, increased therapeutic drug
1137 monitoring and a decrease of up to 90% in the sirolimus
1138 dose may be required (class IIb, level C).
1139

1140 *Evidence Summary*

1141 The introduction of novel antiviral agents in the treat-
1142 ment of HCV has not eliminated the risk of drug interactions.
1143 Physicians should frequently assess for drug–drug in-
1144 teractions in HCV-infected HCT recipients. Many interactions
1145 may not be adequately documented but rather may have to
1146 be inferred on the basis of the isoenzymes responsible for
1147 drug metabolism. Current databases (eg, <http://www.hepdruginteractions.org>) should be consulted along with the
1148 product prescribing information to ensure the safety of
1149 concomitantly prescribed medications such as acid reducers,
1150 antidepressants, antihypertensives, phosphodiesterase in-
1151 hibitors, novel oral anticoagulants, macrolide antibiotics,
1152 triazoles, and HMG CoA inhibitors [1]. However, these da-
1153 tabases lack documentation of potential interactions be-
1154 tween DAAs, commonly prescribed immunosuppressive
1155 agents, and chemotherapy. The pharmacology of DAAs and
1156 potential drug–drug interactions between DAAs and
1157 chemotherapy or immunosuppressive agents used in pa-
1158 tients undergoing HCT are summarized in Table 4 [53–58].
1159

1160 Drug–drug interactions can be pharmacokinetic, result-
1161 ing in changes in drug concentrations, or pharmacodynamic,
1162 resulting in additive, synergistic, or antagonistic effects on
1163 efficacy or toxicity. Metabolism by CYP450 enzyme, specif-
1164 ically the CYP3A4 isoform, is the major metabolic pathway of
1165
1166

Table 4
DAA Pharmacology and Potential Interactions with Drugs Used in HCT

Antiviral Agent*	Metabolism/Elimination	Metabolism Effects	Transporter Substrate	Transporter Effects	Drugs with Which DAA Does or May Interact
Protease inhibitors					
Boceprevir	CYP3A4, aldoreductase	Inhibits CYP3A4	P-gp	Potentially inhibits P-gp	Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels
Paritaprevir (ABT-450) with ritonavir [†]	CYP3A4, CYP3A5	Inhibits CYP3A4, UGT1A1	ABCG2, OATP1B1/3, P-gp	Inhibits ABCG2, OATPB1/3	Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels
Simeprevir	CYP3A4	Inhibits CYP1A2, intestinal CYP3A4	OATP1B1/3, P-gp	Inhibits OATP1B1/3, P-gp	Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels
Telaprevir	CYP3A4	Inhibits CYP3A4	OATP1B1, OATP2B1, P-gp	Inhibits OATP1B1, OATP2B1, P-gp	Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels
Ritonavir [†]	CYP3A4, CYP2D6	Inhibits CYP3A4	P-gp	Inhibits ABCG2	Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels
NS5A inhibitor					
Daclatasvir	CYP3A4	No data	P-gp	Inhibitor of ABCG2, OATP1B1, P-gp	Increase CSA, tacrolimus levels [‡]
Ledipasvir	Oxidized by unknown mechanisms	N/A	ABCG2, P-gp	inhibits ABCG2, P-gp	Increase CSA, tacrolimus levels
Ombitasvir (ABT-267)	Amide hydrolysis, then oxidation	Inhibits UGT1A1	ABCG2, P-gp	substrate only	Unknown
Nonnucleos(t)ide polymerase inhibitor					
Dasabuvir (ABT-333)	CYP2C8 (primary), CYP3A4, CYP2D6	Inhibits UGT1A1	ABCG2, P-gp	Inhibit ABCG2	CYP2D6 inhibitors increase dasabuvir
Nucleos(t)ide polymerase inhibitor					
Sofosbuvir	Extensive hepatic metabolism [§] to active moiety GS-461203, then most is renally eliminated	N/A	ABCG2, P-gp	Substrate only	Unknown
Nucleoside analog					
Ribavirin	Unknown metabolism, 60% renal elimination	N/A	N/A	N/A	Increase myelotoxicity with azathioprine

P-gp indicates P-glycoprotein; OATP1B1/3, organic anion-transporting polypeptides 1B1 and 1B3; OATP2B1, organic anion-transporting polypeptides 2B1; ABCG2, ATP-binding cassette subfamily G member 2; CSA, cyclosporine A; Cy, cyclophosphamide; N/A, not applicable.

* Boceprevir and telaprevir are no longer available in the United States but are still in use in other countries. Ombitasvir, paritaprevir, ritonavir, and dasabuvir are copackaged under the brand name Viekira Pak. Ledipasvir and sofosbuvir are copackaged under the brand name Harvoni.

[†] Ritonavir is used to boost plasma concentrations of paritaprevir.

[‡] Based on the results of drug interaction trials, no clinically relevant changes in exposure were observed for cyclosporine or tacrolimus with concomitant use of daclatasvir [52].

[§] Metabolic pathway involves hydrolysis of carboxyl ester moiety catalyzed by human cathepsin A or carboxylesterase 1 and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway.

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approved HCV therapies, including DAAs. Membrane transporters are also implicated in clinically relevant drug–drug interactions and may include P-glycoprotein, organic anion transporting polypeptides, and the ATP-binding cassette subfamily G member 2. Membrane transporters and the CYP isoenzymes can be induced or inhibited.

The pharmacologic targets of the novel DAAs include NS3/NS4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. The protease inhibitors (paritaprevir, simeprevir, telaprevir, and boceprevir) prevent the NS3 viral protease from cleaving the enzymes responsible for viral replication. All 5 agents undergo CYP3A4 metabolism and are affected by inducers (ie, phenytoin, rifampin, carbamazepine, and phenobarbital) and inhibitors (ie, posaconazole and voriconazole) [18,54–58].

The protease inhibitors may also increase serum concentrations of chemotherapy or immunosuppressive agents commonly used for HCT that are substrates of CYP3A4, including cyclophosphamide, etoposide, tacrolimus, cyclosporine, and sirolimus. Paritaprevir is administered concomitantly with ritonavir, a potent CYP3A4 inhibitor, as a “boosting” agent and will also interfere with other CYP3A4 and CYP2D6 metabolized medications. Thiotepa is an inhibitor of CYP2B6 and has no interactions with DAAs.

The NS5A inhibitors (daclatasvir, ledipasvir, and ombitasvir) inhibit NS5A viral RNA replication and virion assembly. Daclatasvir is metabolized via CYP3A4, whereas ledipasvir and ombitasvir undergo oxidative metabolism [52,55,58]. Ledipasvir is an inhibitor and a substrate of intestinal P-glycoprotein; inducers of P-glycoprotein (ie, St. John’s wort, rifabutin, phenobarbital) that are coadministered may lead to reduced plasma concentrations and therapeutic effects of ledipasvir [58].

The polymerase inhibitor sofosbuvir is renally eliminated, whereas dasabuvir is metabolized via CYP2C8 (major pathway), 3A4, and 2D6 [55]. Sofosbuvir is a substrate of intestinal P-glycoprotein, and inducers of P-glycoprotein (ie, St. John’s wort, rifabutin, phenobarbital) that are coadministered may lead to reduced plasma concentrations and therapeutic effects of sofosbuvir [58].

Immunosuppression with cyclosporine, tacrolimus, and sirolimus is common after HCT. Cyclosporine has been observed to increase sofosbuvir area under the curve (AUC) by 353% [59]. Simeprevir can increase cyclosporine and tacrolimus AUC by 19% and 17%, respectively [60]. Telaprevir increases the dose-normalized exposure $AUC_{0-\infty}$ values of cyclosporine and tacrolimus approximately 4-fold and 70-fold, respectively [61]. The mean half-life of cyclosporine was increased from 12 hours to 42.1 hours, and the mean half-life of tacrolimus was increased from 40.7 hours to 195 hours. Boceprevir increases the $AUC_{0-\infty}$ values of cyclosporine and tacrolimus approximately 3-fold and 17-fold, respectively [62]. Experience with dosing of immunosuppressive agents after liver transplant concomitantly with telaprevir or boceprevir plus IFN and ribavirin suggests an empiric dose reduction of approximately 75% for tacrolimus and 35% for cyclosporine [63,64]. Telaprevir and boceprevir are no longer available in the United States. Sirolimus plasma concentrations with the use of DAAs have not been prospectively evaluated, but case reports in patients with liver transplant would suggest a 90% dose decrease [64].

When a calcineurin inhibitor or sirolimus is used with a protease inhibitor, it is reasonable to empirically reduce the dose of the immunosuppressive agents and monitor their

levels more frequently because of major CYP3A4 and P-glycoprotein drug–drug interactions. Formal dosing recommendations and the degree of dose adjustments in HCT recipients are conservatively estimated because pharmacokinetic studies have not evaluated dosage changes; studies are limited to healthy volunteers or solid organ transplant recipients.

Knowledge Gap

- Studies are needed on the potential interactions between DAAs, immunosuppressive agents, and chemotherapy used in HCT candidates.

OVERLAP BETWEEN TOXIC EFFECTS OF DAAS AND OF CONDITIONING REGIMENS AND SYMPTOMS OF GVHD IN HCV-INFECTED HCT CANDIDATES AND RECIPIENTS: SARAH P. HAMMOND AND SERGIO GIRALT

Recommendations

- No recommendations can be made regarding overlap between the toxic effects of DAAs and the toxic effects of HCT conditioning regimens or symptoms of GVHD because evidence is lacking.

Evidence Summary

Historically, treatment of HCV with IFN and ribavirin in allogeneic HCT recipients was carried out with some trepidation because of concerns about exacerbation of GVHD, anemia, and neutropenia. However, a relatively large cohort study showed no overall increase in GVHD among allogeneic HCT recipients treated with IFN with or without ribavirin after transplant, and there was a trend toward a decrease in the risk of severe liver complications after transplant with HCV treatment [65].

Because DAAs have been approved by the FDA for treatment of HCV only since 2011, information about the use of these agents in allogeneic HCT candidates and recipients is largely anecdotal [1]. This paucity of data limits understanding of the overlap between the toxic effects of DAAs and the toxic effects of HCT conditioning regimens and symptoms of GVHD.

The first DAAs approved to treat genotype 1 HCV infection, telaprevir and boceprevir, were both associated with toxic effects that could be mistakenly attributed to GVHD (eg, rash) or HCT conditioning regimens (eg, anemia) in the appropriate clinical context [66,67]. However, the availability of potent alternatives with fewer side effects to treat genotype 1 HCV has made telaprevir and boceprevir less desirable than other agents (both telaprevir and boceprevir have been removed from the US market) [47,48]. Simeprevir, a more recently approved protease inhibitor, can cause mild hyperbilirubinemia, which could also be mistakenly attributed to GVHD in the appropriate clinical context, but this effect is typically transient [68].

In general, the observed toxic effects of newer DAAs approved for clinical use outside of clinical trials are minimal compared with the toxic effects of IFN, ribavirin, and even telaprevir and boceprevir. Further studies and more post-marketing experience with these medications, particularly in patients with hematologic disorders and patients who have undergone HCT, will be crucial for predicting potential toxic effects unique to HCT recipients.

Knowledge Gap

- The toxicity profile of DAAs in HCT recipients, including the toxic effects on progenitor cells.

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