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Heart Transplantation From Hepatitis C–Positive Donors in the Era of Direct Acting Antiviral Therapy: A Comprehensive Literature Review

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Background. While heart transplantation is a highly effective treatment in patients with advanced heart failure, the number of people waiting for a transplant exceeds the number of available donors. With the advent of direct acting antivirals (DAA) for the eradication of Hepatitis C, the heart transplant donor pool has been expanded to include donors with untreated Hepatitis C. To help with the development of future protocols for Hepatitis C–positive heart transplants, we performed a review of the literature on DAA therapy in the context of heart transplantation. **Methods.** We searched MEDLINE, EMBASE, OVIDE JOURNAL, and GOOGLE SCHOLAR for papers published between 01.01.2011 and 01.06.2019 using key words "heart transplantation" associated with "hepatitis C." **Results.** After removing duplicates, we screened 78 articles and retained 16 for primary analysis and 20 for sustained virologic response 12 weeks after completion of the DAA therapy (SVR-12). The data from 62 patients were extracted from these publications. Fifty-six (90%) patients had donor-derived hepatitis C and 6 (10%) patients were chronically infected with hepatitis C before transplantation. All living transplanted patients achieved SVR-12, defined as hepatitis C virus RNA below the limit of detection 12 weeks after treatment completion. Treatment duration ranged from 4 to 24 weeks. Clinically relevant modification to the dosing of immunosuppressive mediations during DAA therapy was documented in only 1 patient (1.6%). Six (14%) patients experienced rejection during DAA therapy. **Conclusions.** Despite different timings of initiation of DAA therapy across the included studies, there were no differences in sustained viral clearance. Early commencement of DAA with a potentially shorter treatment duration (<8 wk) is appealing; however, further studies are required before recommending this approach.

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While heart transplantation is a highly effective treatment in patients with advanced heart failure, the number of people waiting for transplant exceeds available donors. In the United States alone, up to 350 people die each year awaiting heart transplant,[1] and it has been estimated that if the donor pool was widened to include those with hepatitis C, >140 extra heart transplants could be performed annually.[2]

Hepatitis C virus (HCV) is an enveloped flavivirus with a parenteral mode of transmission.[3] There are 6 viral genotypes with >67 subtypes.[4] Before 2001, screening for hepatitis C in donors and recipients was not routinely performed. This led to numerous donor-derived hepatitis C (DDHC) infections[5] and increased morbidity and mortality.[6,7] As a result, donors with HCV were routinely excluded.

With the arrival of highly-effective direct acting antiviral (DAA) therapy including pan-genotypic DAA, transplantation of hepatitis C–positive donor organs,[8-10] including hearts,[11] has become a viable option. A growing number of protocols addressing this topic are being established and a number of centers are currently following patients who have received organs from HCV-positive donors.[12-16] The most recent International Society of Heart and Lung Transplantation (ISHLT) conference abstracts include the largest published cohorts of transplant recipients undergoing successful

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Hepatitis C treatment[5,17-26]; however, these studies are still on-going.

As expressed in the editorial by Givertz et al,[27] transplantation of hearts from hepatitis C–positive donors (either RNA and/or antibody positive) has presented clinicians with an opportunity to expand the donor pool and close waitlist gaps. It is also an opportunity for marginal recipients to significantly shorten the waiting list times by accepting a heart from a hepatitis C–positive donor. In 1 center, the mean waitlist time was 329 days for those receiving an HCV negative graft and 78 days in those accepting a Hepatitis C–positive graft.[28] In another cohort, the waitlist time for Hepatitis C–positive grafts was as little as 4 days.[5] However, some questions remain unanswered that need to be addressed before heart transplantation from HCV-positive donors becomes the standard of care.

The objective of our review was to analyze the currently published literature to address the following questions: what is the efficacy of DAA in the setting of heart transplantation? What interactions between immunosuppression and DAA have been documented? Does DAA increase the risk of acute rejection? What is the optimal timing for the initiation of DAA? And what is the most favorable duration of therapy?

MATERIALS AND METHODS

Search Method

We utilized PRISMA flow-chart to plan our review.[29] An electronic search was performed in Medline, Embase, Ovide journal, and Google Scholar to identify all articles and abstracts in English, French, and German published between 01.01.2011 and 01.06.2019. We chose this particular time frame to cover the era of direct DAA therapy.

In order to set up the search, we used keywords, automatic generated synonyms (in Ovid), and MESH terms. We searched for "heart transplantation" associated with "hepatitis C" or with "direct-acting antiviral" in the title of the publication. In an attempt to cover all the available literature, we use 3 predefined goals (see Appendix for complete list of terms used in the search and details of internal controls).

Study Identification

All publications, including cohort studies, clinical trials, reviews, case series, case reports, or conference abstracts, were eligible if they documented at least 1 patient being treated with an interferon-free hepatitis C regimen after a heart transplantation. After removing duplicates by comparison of DOI, all abstracts from identified publications were examined for eligibility.

Exclusion criteria were publications about pediatric patients (<18 y old at time of transplantation) and insufficient data completeness (defined as <50% of prespecified patient characteristics available in the full text article). References in the included articles were then searched to identify other studies for inclusion.

Data Extraction

We predefined 23 patient and treatment characteristics and searched for them manually in each of the retained publications. The main items were source of infection; time lapse between transplantation and start of DAA; regimen used; follow-up of the viral load; type of immunosuppressive therapy for initial induction and maintenance; reported interactions between DAA and immunosuppressive therapy; and rejection episodes described during treatment (see Appendix for a completed list of extracted data).

RESULTS

Publication Selection and Quality Control

An electronic search identified 146 publications. After removing duplicates, 78 publications were screened and 34 met inclusion criteria. After reading the papers, 14 publications were excluded—3 were in a pediatric population[30] and the other 11 had insufficient data for analysis.

The PRISMA-chart is provided in Figure 1 and the list of publications included is detailed in Table 1.

Some studies that had preliminary results presented as published abstracts at the 2019 ISHLT meeting represent important recent work, and a large number of patients who have

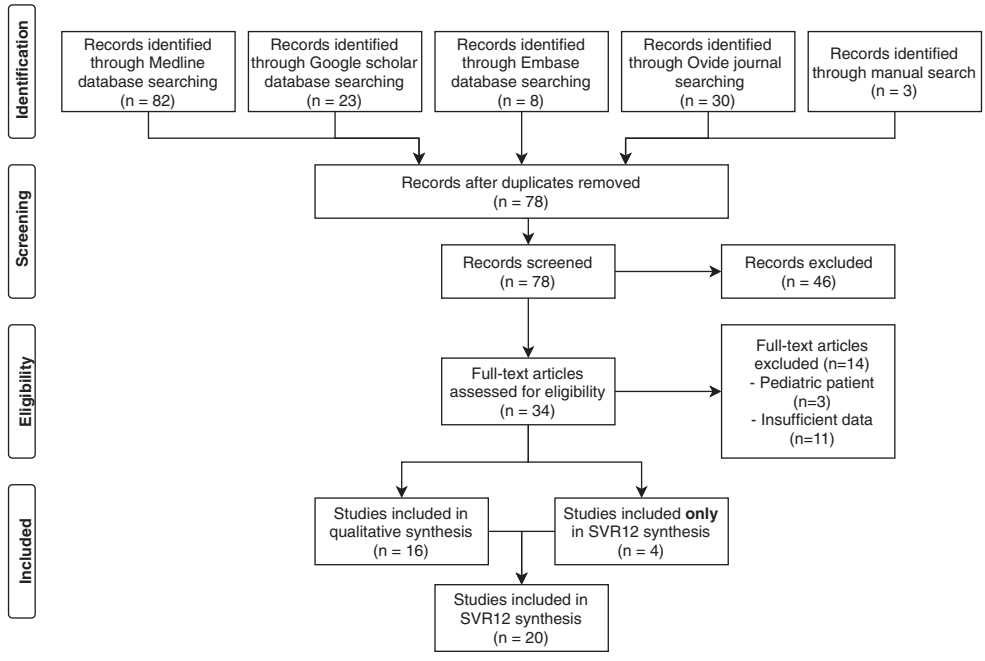

FIGURE 1. PRISMA flow-chart. SVR12, sustained viral response after 12 wk.

TABLE 1.

List of included publications

Reference	Y of publication	Country	Number of patients	Timing of DAA therapy initiation[g]	DAA	SVR-12 (n)	Immunosupression	Reported interactions with IS	Reported major AE related to DAA (n)
Trakroo and Qureshi[31]	2015	US	1	Late	SOF/SIM	Yes (1)	TAC; MYC	No	No
Casanovas et al[32]	2015	Spain	1	Late	DCV/SIM	Yes (1)	EVE	No	No
Liu et al[33]	2016	Taiwan	1	Delayed	LDV/SOF	Yes (1)	NR	No	No
Grinstein et al[34]	2017	US	1	Delayed	LDV/SOF	Yes (1)	NR	No	No
Liu et al[35]	2017	Taiwan	12	NR	DCV/SOF	Yes (12)	NR	Yes[c]	No
Vitrone et al[36]	2017	Italy	2	Late	DCV/SOF	Yes (2)	CsA; EVE; PRED (1) TAC; MYC; PRED(1)	Yes[b]	No
Gottlieb et al[37]	2017	US	1	Delayed	SOF/VEL	Yes (1)	TAC; MYC; PRED	No	No
Wettersten et al[38]	2018	US	1	Delayed	ELB/GRA	Yes (1)	TAC; MYC; PRED	No	No
Alam et al[39]	2018	US	1	Delayed	LDV/SOF	Yes (1)	NR	No	No
Aslam et al[40]	2018	US	6	Delayed	GLE/PIB(2) ELB/GRA(3) SOF/VEL(1)	Yes (6)	TAC; MYC; PRED	No	No
Jawad et al[41]	2018	Germany	1	Late	DCV/SOF	Yes (1)	CsA; EVE	No	No
Schlendorf et al[42]	2018	US	9	Delayed	LDV/SOF(7) SOF/VEL(2)	Yes (8)[d]	CsA; MYC; PRED	No	No[d]
Moayedi et al[43]	2018	US	2	Delayed	LDV/SOF(1) SOF/VEL(1)	Yes (2)	TAC	No	No
McLean et al[44]	2019	US	10	Early	ELB/GRA	Yes (9)[e]	TAC; MYC; PRED	No	No[e]
Woolley et al[11]	2019	US	7[a]	Preemptive	SOF/VEL	Yes (7)	TAC; MYC; PRED	No	No
Frager et al[45]	2019	US	6	Delayed	EBR/GZR(2) GLE/PIB(3) SOF/VEL	Yes(5) No(1)	TAC; MYC; PRED	No	Hepatitis[f]

[a]Eight patients received a heart transplant in this study; data were only available for 7 of them who completed 6 mo of follow-up. The last patient was alive at the date of publication but had not completed the 6 mo of follow-up.
[b]Decrease of Everolimus level necessitating an up titration.
[c]Change in tacrolimus level without any change to the drug dose.
[d]One patient died during DAA therapy of massive lung embolism, but had a negative HCV RNA result prior.
[e]One patient died during DAA therapy of multiorgan failure after an antibody mediated rejection and also had a negative RNA result prior.
[f]Biopsies proven medicament-related hepatitis in a patient treated with herbal remedy (unspecified), immunosuppression, and DAA.
[g]Prophylactic: on the day of HTX; Early: first wk after HTX; Delayed: first 3 mo after HTX or after discharge; Late: >3 mo after HTX
DAA, direct acting antiviral; DCV/SIM, daclatasvir/simeprevir; DCV/SOF, daclatasvir/sofosbuvir; ELB/GRA, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HTX, heart transplantation; LDV/SOF, ledipasvir/sofosbuvir; NR, not reported; PRED, prednisone; SOF/SIM, simeprevir/sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir; SVR-12, sustained viral response after 12 wk.

been successfully treated. Though not suitable for our primary analysis, they provide important information about this topic and will be invaluable once the studies are fully completed. Four of them were integrated into the analysis of sustained viral response after 12 weeks (SVR-12). The summary of ongoing studies is shown in Table 2.

The 16 included studies consisted of 2 abstracts (Congress abstract/presentation), 7 case reports, 3 case series, and 4 cohort studies. The completeness of data provided was rated as sufficient in 5 (31%) publications and as good in the remaining 11 (69%).

Characteristics of the Publications

Eleven out of 16 publications (68%) were written by research groups working in institutions in the United States.

Epidemiology and Characteristics of the Patients/Transplant/HCV

Selected epidemiological and descriptive characteristics of the transplant recipients are described in Table 3. Four patients (8%) underwent a multiorgan transplantation, 3 of these patients (6%) received a combined heart-kidney transplant[38,40,45] and 1 patient (2%) received a heart-liver transplant.[34] The majority of patients (n = 16, 47%) received basiliximab as induction. The most commonly used maintenance immunosuppression was a combination containing tacrolimus (91%). Most centers used the same induction and maintenance immunosuppression protocol as per their usual practice without changing the dose or the timing of the immunosuppressive drugs.[44]

Data relating to the nature of the hepatitis C infection are shown in Table 4. DDHC was the principal mode of infection (n = 56, 82%), including 5 patients previously infected with hepatitis C and cured (documented by negative nucleic acid testing [NAT], then reinfected by a NAT-positive heart during transplantation [DDHC*]). Another 6 patients (10%) were transplanted while having known, active HCV. None of the patients received DAA prophylactically. Seven patients (14%) were treated preemptively (starting day 1 posttransplant) and 10 patients (20%) received therapy during the first week posttransplant. The majority were treated after the first week posttransplant; 28 (56%) in the first 3 months after transplantation and five (10%) >3 months after transplant (ranging from 6 mo to 14 y).

Eight different DAA regimes were used. A pan-genotypic regimen was used in 15 (21%) of all treated patients. Forty-five (80%) were treated for 12 weeks. In 7 patients (13%), 4 weeks of treatment was used.[11]

Type of DAA Therapy

The types of DAA regimens are shown in Table 3. The different regimens reflect differences in local policies and timing

TABLE 2.

List of abstract from ongoing study

Reference	Y of publication	Country	Patients (n)	Included in SVR-12 analysis	SVR-12 (n)	Conclusion of the authors to this date
Lebeis et al,[19] Gaj et al,[23] and Lewis et al[24]	2019	US	23	No	Not published	"(…)patients who underwent HCV-positive donor heart transplantation received hearts at lower sequence numbers with a trend toward lower donor age. Short-term outcomes with HCV-positive donor hearts are favourable(…)"[23] "(…)patients who received preemptive direct-acting antiviral therapy following receipt of an HCV-positive donor heart demonstrated preserved early allograft function post-transplant."[19] "(…)Preemptive administration of well-tolerated oral pan-genotypic direct-acting antiviral therapy results in expedited organ transplantation, rapid HCV suppression and the prevention of chronic HCV infection in patients receiving HCV-infected donor hearts.(…)"[24]
Gidea et al[18,20] and Reyentovich et al[26]	2019	US	25	No	Not published	"(…) heart transplantation from donors with active hepatitis C is safe with excellent short term survival and rapid clearance of viremia.(…) Long-term follow up is necessary."[26] "Heart transplantation from donors with active hepatitis C is safe with rapid clearance of viremia in all exposed patients. Time to viral clearance is related to initial viremic load.(…)"[20] "Early biopsy of heart transplantation from donors with active hepatitis C is not associated with high grade cellular or any humoral rejection. The 1R/2A rejections seems to be more frequent in the HCV group and did not correlate with the level of viremia(…)"[18]
Wolfe et al[25]	2019	US	11	Yes for 5 patients	Yes (5); not published (6)	"We present real world experience about the implementation of a protocol allowing HCV and HBV NAT+ donors to be used for thoracic and multivisceral transplants.(…)"[25]
Schlendorf et al,[5] Chowdhury et al,[22] and Zalawadiya et al[46]	2019	US	49	Yes for 27 patients	Yes (27); not published (22)	"In the era of highly effective HCV pharmacotherapy, the use of HCV-exposed donors safely allows for expansion of the donor pool."[5] "Recipients of hearts from HCV donors have promising long-term outcomes. However, we report 2 cases of hemorrhagic pancreatitis that developed in patients with HCV infection before therapy with DAAs. Further studies are needed to elucidate the potential association between HCV infection in immunosuppressed hosts, and acute pancreatitis."[22] "(…)Larger scale data on changes in MIT is required to appropriately assess the effect of dd-HCV infection on incident CAV."[46]
Morris et al[21]	2019	US	10	Yes for 5 patients	Yes (5); not published (10)	"(…) We have demonstrated feasibility of utilizing viremic HCV donor hearts for organ transplantation (…)"[21]
Aslam et al[17]	2019	US	18	Yes for 10 patients	Yes (9); patient died (1); not published (8)	"(…) There is utility in using such organs to expand the current donor pool. Further long-term follow-up is needed."[17]

DAA, direct acting antiviral; dd-HCV, donor-derived hepatitis C; HCV, hepatitis C virus; MIT, maximum intima thickness; NAT, nucleic acid testing; SVR-12, sustained viral response after 12 wk.

of availability of various DAA. Despite the heterogeneity of DAA regimens no difference in HCV clearance was demonstrated, with all patients clearing the virus.

Efficacy of DAA Therapy

All patients treated with a complete course of DAA achieved RNA clearance between 1 and 12 weeks of therapy (Table 5).

Median time to clearance was 4 weeks. All surviving patients with available data achieved as SVR-12, which is an accepted criterion to determine HCV cure.[47] One patient failed to reach viral clearance after cessation of the DAA drug in the context of a medication induced hepatitis.[45] The longest follow-up was 18 months after DAA therapy with persistently negative RNA. No relapses were documented.

Complications and Drug Interactions During DAA Therapy

The presence of non-life-threatening complications was not systematically reported. In the publications that did report non-life threatening morbidity data, the adverse event rate was ~60% of patients,[35] which is slightly lower than the adverse event rates reported in the Phase 3 DAA treatment studies.[48]

Major complications are shown in Table 6. Three patients died during follow-up: 1 (1%) due to a massive pulmonary embolus, 1 (1%) due to multiorgan failure after antibody-mediated rejection, and 1 (1%) due to disseminated bacterial infection. All events were adjudicated by the study teams as not related to HCV infection or DAA therapy. Six (16%) patients suffered from rejection during DAA therapy; all occurred <3 months following transplantation. Changes in immunosuppressive drug levels were reported in 2 (7%) patients. In 1 patient, the DAA was ceased secondary to medication-induced hepatitis. This patient was concomitantly on a DAA, a herbal supplement and azole therapy for an opportunistic infection. We cannot exclude the role of the DAA in this scenario; however, both herbal supplements and azole therapy can provoke a clinical picture of hepatitis. The cessation of the DAA resulted in an ongoing DDHC and this patient needed to be treated with 3 different DAA regimes over a prolonged period to be cured of the infection.[45]

TABLE 3.

Characteristic of patients and transplantation included in the analysis

	Number of patients with available data (total N=62 patients)	
	n (%)	n (%)
Age of patients (mean, y)[a]	49 (7)	53
Etiology of heart failure	21 (33)	
DCM		11 (52)
HCM		5 (23)
ICM		3 (14)
LV non-compaction		1 (04)
Graft failure after HTX		1 (04)
LVAD implantation before HTX	38 (61)	
No		24 (63)
Yes		14 (36)
Multiorgan transplantation	50 (80)	
No		41 (93)
Yes		4 (08)
Induction use	34 (54)	
Basiliximab		16 (47)
No induction		8 (23)
No induction		7 (20)
Basiliximab + ATG		2 (05)
Corticosteroid		1 (02)
Immunosuppressive drugs	47 (75)	
Tacrolimus		43 (91)
Prednisone		42 (89)
Mycophenolate		41 (87)
Everolimus		4 (06)
Cyclosporin		3 (06)
Azathioprine		1 (02)

[a]At the beginning of DAA therapy.
ATG, Anti-thymocyte globulin; DAA, Direct Acting Antiviral; DCM, Dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; HTX, Heart transplantation; LVAD, Left ventricular assist device.

TABLE 4.

Hepatitis C characteristics and treatment

	Number of patients with available data (total N=62 patients)	
	n (%)	n (%)
Source of HCV infection	62 (100)	
DDHC		51 (82)
DDHC*		5 (08)
PTHC		6 (10)
Genotype	54 (87)	
1a		24 (44)
1b		12 (22)
1		5 (09)
2		2 (04)
3		6 (11)
4		4 (07)
6		1 (02)
Timing of DAA therapy initiation[a]	50 (81)	
Prophylactic		0 (00)
Preemptive		7 (14)
Early		10 (20)
Delayed		28 (56)
Late		5 (10)
DAA regime	62 (100)	
LDV/SOF		18 (29)
ELB/GRA		14 (23)
DCV/SOF		13 (21)
SOF/VEL[b]		8 (13)
GLE/PIB[b]		5 (08)
EBR/GZR		2 (05)
DCV/SIM		1 (02)
SOF/SIM		1 (02)
Duration of the initial DAA therapy (wk)[c]	56 (90)	
4		7 (13)
12		45 (80)
16		1 (02)
24		3 (05)

[a]Prophylactic: on the day of HTX; Early: first wk after HTX; Delayed: first 3 mo or after discharge; Late: >3 mo after HTX.
[b]Pan-genotypic regimen.
[c]If >1 therapy was used, duration of the first cured. Only 1 patient received to treatment course with DAA, sadly the duration of the first course of treAement is not known.
DAA, direct acting antiviral; DCV/SIM, daclatasvir/simeprevir; DCV/SOF, daclatasvir/sofosbuvir; DDHC, donor derived HCV; DDHC*, patient with previously cured HCV (proven by negative NAT) and re-infection (proven by positive NAT); EBR/GZR, elbasvir/grazoprevir; ELB/GRA, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HTX, heart transplantation; LDV/SOF, ledipasvir/sofosbuvir; NAT, nucleic acid testing; PTHC, pretransplant HCV infection; SOF/SIM, simeprevir/sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir.

One study reported an interaction between ledipasvir/sofosbuvir and everolimus that required a dose reduction of the everolimus.[35] Another study reported an interaction between daclatasvir/sofosbuvir(DCV/SOF) and both mycophenolate and tacrolimus resulting in a slightly decreased level of tacrolimus and an increased level of mycophenolate without requiring any dose adjustments.[36]

There were no documented cases of an interaction between DAA and the induction regime in our series.

DISCUSSION

What Is the Efficacy of DAA in the Setting of Transplantation?

In the setting of transplantation, DAA therapy appears to be safe and effective for the treatment of HCV. Despite the heterogeneity of the studies, there was no reported HCV relapse following complete DAA therapy. Nevertheless, it is worth noting that continued monitoring of viral loads posttreatment was reported in most series. In the THINKER trial that reported on kidney transplants from HCV-viremic donors to HCV-negative recipients, 1 patient had increased HCV viral loads on follow-up measurements during therapy because of DAA resistance and required a change in his DAA therapy.

Due to geographic variations in the prevalence of HCV genotypes, differences exist in national guidelines on the use of DAA for HCV. American guidelines recommend the use of a genotype-guided therapy,[49] whereas in Australia a pan-genotypic combination is recommended as first-line treatment.[50] Despite the differences in choice of DAA combinations, timing of initiation and duration of DAA therapy between studies, all studies reported 100% cure rate. None of the studies identified in this review reported prophylactic administration of DAA (commencing pretransplant) and only 1 study reported the use of a preemptive protocol in the first week posttransplant. Most studies documented HCV infection of the recipient (by NAT testing) before commencement of DAA therapy. This likely reflects the high cost of DAA therapy and the reimbursement arrangements that exist in countries where there

TABLE 5.

Results of HCV therapy in all published data

	Number of patients with available data (total N=109 patients)
	n (%)
Demonstrated negative NAT during the initial DAA therapy[b]	108 (99)
SVR-12 after the initial DAA therapy	104 (96)[a]
Recurrence of positive NAT after documentation of negative NAT during DAA therapy	0 (00)

[a]Three patients died during DAA therapy, all with demonstrated negative RNA result prior, SVR-12 not available in 1 publication,[11] 1 patient failed to demonstrate negative NAT during the first course of DAA therapy in the context of DAA interruption.[45]
[b]One patient failed to demonstrate negative NAT during the first course of DAA therapy in the context of DAA interruption.[45]
DAA, direct acting antiviral; HCV, hepatitis C virus; NAT, nucleic acid testing; SVR-12, sustained viral response after 12 wk.

TABLE 6.

Complications during HCV therapy

	Number of patients with available data (total N=62 patients)	
	n (%)	n (%)
Graft failure/rejection during DAA therapy[a]	46 (74)	
No		40 (86)
AMR		1 (02)
AMR + ACR		1 (02)
ACR		4 (10)
Graft dysfunction during DAA therapy	15 (24)	0 (00)
Vital status at 12 wk	62 (100)	
Alive		59 (95)
Death		3 (5)
Relevant change in immunosuppressive level	34 (54)	
No		32 (94)
Yes		2 (06)

[a]ACR were considered if more than ISHLT-1R
ACR, acute cellular rejection; AMR, antibody mediated rejection; DAA, direct acting antiviral; HCV, hepatitis C virus; ISHLT, International Society of Heart and Lung Transplantation.

is a requirement to prove HCV infection before commencing DAA therapy.

In the case of transplantation the use of a pan-genotypic is probably the optimal approach for prophylactic and preemptive treatment because of the expected delay in obtaining the genotype of the donor. It is worth noting that a pan-genotypic treatment is being utilized in 2 ongoing studies of DAA after transplantation as well as the most recent publication on the topic.[11,12,16,24]

What Interactions Between Immunosuppression, Induction Regime and DAA Have Been Observed?

The data regarding pharmacokinetic interactions between DAA and immunosuppression are also reassuring. Initiation of the DAA resulted in a significant change to biochemical drug levels in only 2 of 62 patients (3%); however, neither of these patients developed rejection. In an abstract addressing this question, no adjustment of immunosuppression was needed after DAA therapy was started.[51] A recently published review on immunosuppression levels in patients undergoing DAA therapy confirmed this probable lack of interaction. No change in the drug levels were observed retrospectively when DAA were started.[51]

Moreover, if DAA therapy is administered early after transplantation, the risk of persistent sub- or supra-therapeutic levels of immunosuppression drugs is greatly reduced as immunosuppressive drug levels are routinely checked and titrated at regular intervals during this time period.

In this series, most of the patients (16 patients, 47%) received basiliximab as induction and no interaction between induction and DAA were reported, but it is worth mentioning that most of the patients (n = 33, 66%) did not receive DAA during the first week after transplantation. With the half-life of 30 days for Anti-thymocyte globulin (ATG)[52] and 7 days for basiliximab, the absence of interaction between DAA and induction regime must be reviewed with some caution.

Does DAA Therapy Increase the Risk of Acute Rejection?

The risk of rejection due to the HCV viral load or treatment with DAA cannot be formally determined from published studies due to the heterogeneity of the data. However, 6 (14%) patients suffered from acute cellular or antibody-mediated rejection over the course of the DAA therapy. The rate of acute rejections in these studies is comparable with the available data on rejection in the absence of HCV or DAA.[53]

In a cohort of 25 patients, there was no significant difference in the observed rate of rejection (ISHLT grad >1R) between patients with DDHC and a control group. No correlation between viral load and rejection could be found.[18] The long-term risk of chronic rejection is for the moment mostly unknown. One group has shown that patients who are viremic before initiation of DAA treatment have more marked intimal thickening shown on intravascular ultrasound of the left anterior descending coronary artery.[46]

What Is the Optimal Timing of the Initiation and Duration of DAA Therapy?

The optimal timing of initiation of DAA and the duration of the therapy in the setting of transplantation of a noninfected patient with a HCV-infected heart is still not established.

In the patients reported in this review, most commenced treatment at first documentation of viremia. Seven patients (14%) received preemptive therapy (first day after transplantation) and none received prophylactic treatment as has been described in a recently published kidney transplant protocol[9,10] and ongoing heart transplant study.[24] As seen in the current review, the success of DAA therapy does not seem to be affected by the timing of initiation. Nevertheless, the long-term consequences of the initial viremic period are unknown, particularly the risk of hepatitis C-induced coronary arteriosclerosis,[46,54] and the possibility of accidental transmission to medical staff should also be considered. In the context of immunosuppression, initial viremia may be extremely high and this could have negative consequences. Some data suggest a deleterious effect of the viremic load on the incidence of ISHLT-1R mild rejection (but not moderate and severe rejection)[18] and there are 2 case reports of possible DDHC-associated pancreatitis in patient with high viral load before commencing DAA therapy.[22]

As demonstrated with kidney transplantation in the same setting, a prophylactic dose or a preemptive dose (given few h after transplant) could diminish or even completely suppress viral load.[9-11]

Regarding duration of therapy, international guidelines on DAA for HCV treatment recommend a duration of 8–12 weeks depending on the DAA regimen.[55,56] The most recently published study on heart (and lung) transplantation from HCV-infected donors utilized a 4-week protocol of preemptive therapy with a pan-genotype combination commencing within hours of transplantation.[11] Interestingly, nearly all recipients had detectable hepatitis C viremia immediately posttransplant but all patients achieved sustained viral clearance with no late relapses. While this study suggests that preemptive initiation of treatment may allow a shorter course of DAA to be administered, only 8 heart transplants were included in the study. A confirmatory study in a larger cohort of patients would be desirable before routinely advocating this regimen.

Limitations

Given the observational nature of all the studies included in this review, there is a possible publication bias in favor of studies with positive outcomes. Nonetheless, the highly consistent conclusions of all published studies in relation to the efficacy of DAA and favorable clinical outcomes of heart transplant recipients with DDHC provides compelling evidence to support the use of NAT-positive hepatitis C donors for heart transplantation. Our review did not address the safety of heart transplantation from NAT-negative hepatitis C–seropositive donors; however, published data show that the risk of transmission of hepatitis C from these donors is very low.[57]

CONCLUSIONS AND RECOMMENDATIONS

Based on this systematic review, we make the following conclusions and propose the following recommendations regarding protocols for heart transplantation from HCV viremic donors to HCV-negative recipients:

- While all DAA regimens achieve excellent cure rates for HCV infection, in view of the high rate of acute kidney injury in the first weeks after heart transplantation, we recommend the use of a pan-genotypic drug combination that is eliminated by the liver.
- Despite different timings of initiation of DAA therapy across the included studies, there were no differences in sustained viral clearance. Early commencement of DAA with a potentially shorter treatment duration (< 8 wk) is appealing; however, further studies are required before recommending this approach.
- No patients developed viral resistance or treatment failure when DAA was used according to the protocol. One patient failed therapy after an interruption of therapy. We recommend that all patients undergo serial NAT testing during the first weeks of treatment until their HCV RNA is below the limit of detection to either confirm viral clearance or detect treatment failure. Twelve weeks after cessation of the treatment, regardless of the duration of therapy, a last NAT should be performed to confirm SVR-12.
- No preemptive changes in induction and maintenance immunosuppression are needed. Interactions between DAA and immunosuppression do exist but appear rare. Data on the interaction between induction and DAA are scarce, but the literature on the use of Basiliximab with DAA suggests it is safe to use. When DAA is initiated during the early phase after transplantation, immunosuppressive drug levels are routinely measured until a stable dose of immunosuppression is found. In this context, the risk of dangerously low or high levels of immunosuppression is minimal. However, when DAA therapy is completed, immunosuppressive medication levels should be monitored in case of changes related to cessation of the therapy.
- For recipients of NAT-negative hepatitis C-seropositive (ie, antibody positive) donors, a "watchful waiting" protocol with serial NAT testing up to 3 months posttransplant is recommended.
- Because the risk of coronary intimal thickening is known for patient with chronic hepatitis C and because some data suggest that patient with DDHC and initial viral load have some intimal thickening on intravascular ultrasound at 1 years, a careful assessment of vasculopathy in this population is suggested.

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