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Expanding the Deceased Donor Pool in Manitoba Using Hepatitis C-Viremic Donors: Program Report

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Abstract

Purpose of program: The ongoing shortage of organs for transplant combined with Manitoba having the highest prevalence of end-stage renal disease (ESRD) in Canada has resulted in long wait times on the deceased donor waitlist. Therefore, the Transplant Manitoba Adult Kidney Program has ongoing quality improvement initiatives to expand the deceased donor pool. This clinical transplant protocol describes the use of prophylactic pan-genotypic direct-acting anti-viral agents (DAA) for transplanting hepatitis C (HCV)-viremic kidneys (HCV antibody positive/nucleic acid [nucleic acid amplification testing, NAT] positive) to HCV-naïve recipients as routine standard of care. We will evaluate the provincial implementation of this protocol as a prospective observational cohort study.

Sources of information: Scoping literature review and key stakeholder engagement with interdisciplinary health care providers and health system leaders/decision markers.

Methods: Patients will be screened pre-transplant for eligibility and undergo a multilevel education and consent process to participate in this expanded donor program. Incident adult HCV-naïve recipients of an HCV-viremic kidney transplant will be treated prophylactically with glecaprevir-pibrentasvir with the first dose administered on call to the operation. Glecaprevir-pibrentasvir will be used for 8 weeks with viral monitoring and hepatology follow-up. Primary outcomes are sustained virologic response (SVR) at 12 weeks and the tolerability of DAA therapy. Secondary outcomes within the first year post-transplant are patient and graft survival, graft function, biopsy-proven rejection, HCV transmission to recipient (HCV NAT positive), and HCV nonstructural protein 5A (NS5A) resistance. Safety outcomes within the first year post-transplant include fibrosing cholestatic hepatitis, acute liver failure, primary and secondary DAA treatment failure, HCV transmission to a recipient's partner, elevated liver enzymes ≥2-fold, abnormal international normalized ratio (INR), angioedema, anaphylaxis, cirrhosis, and hepatocellular carcinoma.

Key findings: This program successfully advocated for and obtained hospital formulary, provincial Exceptional Drug Status (EDS), and Non-Insured Health Benefits (NIHB) to provide prophylactic DAA therapy for this indication, and this information may be useful to other provincial transplant organizations seeking to establish an HCV-viremic kidney transplant program with prophylactic DAA drug coverage.

Limitations: (1) Patient engagement was not undertaken during the program design phase, but patient-reported experience measures will be obtained for continuous quality improvement. (2) Only standard criteria donors (optimal kidney donor profile index [KDPI] ≤60) will be used. If this approach is safe and feasible, then higher KDPI donors may be included.

Implications: The goal of this quality improvement project is to improve access to kidney transplantation for Manitobans. This program will provide prophylactic DAA therapy for HCV-viremic kidney transplant to HCV-naïve recipients as routine standard of care outside a clinical trial protocol. We anticipate this program will be a safe and effective way to expand kidney transplantation from a previously unutilized donor pool.

Abrégé

Objectif du programme: La pénurie actuelle d'organes à transplanter, combinée au fait que le Manitoba est la province qui présente la plus forte prévalence d'insuffisance rénale terminale au Canada, entraîne de longs délais sur la

liste d'attente d'un organe provenant d'un donneur décédé. Le programme de transplantation rénale pour les adultes du Manitoba (Transplant Manitoba Adult Kidney Program) a mis en place des initiatives d'amélioration continue de la qualité afin d'élargir le bassin de donneurs décédés. Ce protocole clinique de transplantation décrit l'emploi, comme traitement habituel, d'agents antiviraux directs (AAD) pan-génotypiques prophylactiques pour la transplantation de reins provenant de donneurs infectés par le virus de l'hépatite C (VHC) (individus positifs pour les anticorps VHC et acides nucléiques [NAT]) à des receveurs naïfs pour VHC. La mise en œuvre provinciale de ce protocole sera évaluée en tant qu'étude de cohorte prospective et observationnelle.

Sources: Examen de la documentation et évaluation de l'engagement des principaux intervenants avec les fournisseurs de soins de santé interdisciplinaires et les dirigeants/décideurs du système de santé.

Méthodologie: L'admissibilité au programme sera évaluée avant la greffe. Pour participer à ce programme élargi de donneurs, les patients devront se soumettre à un processus d'information et de consentement à plusieurs niveaux. Les adultes incidents naïfs pour VHC devant recevoir un rein virémique-VHC seront traités de façon prophylactique par glécaprévir+pibrentasvir; la première dose administrée au moment de l'appel pour l'opération. Le traitement par glécaprévir+pibrentasvir sera administré pendant 8 semaines avec surveillance virale et suivi hépatologique. Les principaux résultats évalués seront une réponse virologique prolongée (RVP) à 12 semaines et la tolérance au traitement par AAD. Les résultats secondaires mesurés dans la première année suivant la greffe seront la survie du patient et du greffon; la fonction du greffon; le rejet avéré par biopsie; la transmission du VHC au receveur (positif pour VHC et NAT) et la résistance aux protéines non structurelles 5A (NS5A) du VHC. Les résultats relatifs à l'innocuité dans la première année suivant la greffe comprennent la cholestase hépatique fibrosante; l'insuffisance hépatique aiguë; l'échec primaire et secondaire du traitement par AAD; la transmission du VHC au partenaire d'un receveur; une élévation supérieure à 2 fois du taux d'enzymes hépatiques; un INR anormal; un angio-œdème; l'anaphylaxie; une cirrhose ou un carcinome hépatocellulaire.

Principaux résultats: Le programme a recommandé et obtenu l'inscription du traitement prophylactique par AAD sur la liste de médicaments des hôpitaux pour cette indication, en plus du statut de médicament d'exception provincial et de son ajout au Programme des services de santé non assurés (SSNA). Ces renseignements pourraient être utiles à d'autres organismes provinciaux de transplantation qui cherchent à mettre en œuvre un programme de transplantation rénale virémique-VHC avec un traitement prophylactique par AAD.

Limites: (1) La participation des patients n'a pas été entreprise pendant la phase de conception du programme, mais des mesures de l'expérience des patients seront obtenues pour l'amélioration continue de la qualité. (2) Seuls les donneurs satisfaisant aux critères standards (Kidney Donor Profile Index [KDPI] $\leq$ 60) seront inclus. Si cette approche est sécuritaire et faisable, des donneurs de KDPI plus élevés pourront être inclus.

Conclusion: L'objectif de ce projet d'amélioration de la qualité est d'améliorer l'accès aux transplantations rénales pour les Manitobains. Ce programme offrira un traitement prophylactique aux AAD pour les greffes de reins virémiques-VHC à des receveurs naïfs pour VHC comme traitement de référence habituel en dehors d'un protocole d'essai clinique. Nous pensons que ce programme sera un moyen sûr et efficace d'étendre la transplantation rénale à partir d'un bassin de donneurs auparavant non utilisés.

Keywords

high infectious risk donor, direct-acting anti-viral agents, glecaprevir-pibrentasvir, nucleic acid testing, hepatitis C

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Introduction

Transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD) given the high mortality rate on dialysis.[1,2] Transplant has consistently been shown to improve patient survival,[3,4] with earlier transplantation resulting in the best outcomes for survival and quality of life.[4] Many studies have shown a survival benefit with transplant across the age spectrum; however, this benefit becomes attenuated with prolonged time on dialysis.[4,5] Unfortunately, organ scarcity is leading to an increasing waitlist for transplant. Indeed, the number of individuals needing transplant has increased while the number of living and deceased donors has remained relatively constant, resulting in a growing mismatch between organ supply and demand.[6] Manitoba has the highest prevalence and rate of ESRD in Canada, resulting in some of the longest wait times for transplant despite similar rates of transplantation.[7,8] Therefore, efforts are ongoing to expand the donor pool,[6,9] such as expanding the donation after circulatory death (DCD)[10] and accepting marginal[6,11,12] or higher infectious risk donors.[6,9,13]

Changing Perspective on HCV-Positive Organ Donors

Hepatitis C virus (HCV) positive donors were previously excluded from organ donation unless they were being used for HCV-positive recipients, and they have had a higher rate of decline or discard.[14] Recently, the availability of highly sensitive nucleic acid amplification testing (NAT) and direct-acting anti-viral agents (DAA) for HCV has changed the landscape of organ utilization from HCV-positive donors. Nucleic acid amplification testing enables timely differentiation of HCV antibody-positive donors (prior infection with HCV) into actively viremic (NAT-positive) versus non-viremic (NAT-negative). Pan-genotypic DAA therapy for HCV has >95% cure rates, minimal toxicity, good tolerability, short treatment duration, and is highly cost-effective.[15-18] Furthermore, the pan-genotypic glecaprevir-pibrentasvir can be safely used in renal impairment, including hemodialysis and post-renal transplant. The high cure rates with DAA-HCV therapy have resulted in more programs and recipients being willing to accept organs from HCV-positive donors for transplant.[19] While there is an increased infectious risk, these kidneys are often from younger and otherwise healthier donors with a potential for high-quality transplants.[20,21] Taken together, efforts to safely expand the deceased kidney pool using HCV-positive donors have been undertaken by a number of programs to improve outcomes for patients with ESRD.[9,22]

Risks of Transmission From HCV-Positive Donors to HCV-Naïve Recipients

The risk of HCV transmission from non-viremic kidney donors with a positive HCV antibody is low. One study reported a transmission rate of 1.9%, in the setting of a false-negative NAT at the time of donation.[20] Pooling available data from HCV non-viremic donors, including the single false-negative NAT case, there is an overall transmission rate of 1.1%.[20,21,23] When donor viremia has been adequately excluded with HCV NAT testing, there have been no documented cases of transmission from non-viremic donors to HCV-naïve recipients.[18,20,21,23] Due to the low risk of transmission for non-viremic donors, they have been used to transplant HCV-naïve recipients as routine care with close viral monitoring since 2019 in Manitoba.

In contrast, the transmission rate from an HCV-viremic donor is reported to be 100% in HCV-naïve recipients when DAA therapy is not initiated immediately after transplant.[24,25] However, given the significant survival benefit from transplant, HCV-viremic to HCV-naïve transplant with concomitant DAA therapy can improve outcomes for patients with ESRD because transmission can be prevented by prophylactic DAA therapy and there is a high cure rate for post-transplant patients with established infection.[22,24,26] HCV-viremic donors have also been safely used in HCV-naïve recipients across the spectrum of solid organ transplantation.[25,27,28] Indeed, data suggest that perioperative treatment with DAA is safe and effective for achieving sustained virologic response (SVR) in heart, lung, liver, and kidney recipients.[25,27-29]

Kidney Transplantation From HCV-Viremic Donors to HCV-Naïve Recipients

THINKER (2017) was an open-label, single-group, feasibility trial that used HCV genotype 1 viremic donors for kidney transplant of HCV-naïve recipients.[25] All 10 recipients became NAT-positive on POD 3 and subsequently received elbasvir-grazoprevir therapy for 12 weeks. No recipients had nonstructural protein 5A (NS5A) resistance and all achieved SVR.[25] EXPANDER (2018) was an open-label non-randomized trial that used HCV viremic kidneys for HCV-naïve recipients, with elbasvir-grazoprevir started preoperatively.[28] Recipients of HCV genotype 1 kidneys continued elbasvir-grazoprevir for 12 weeks, while those with genotype 2 or 3 had sofobusvir added to elbasvir-grazoprevir for 12 weeks of triple therapy. All 10 recipients achieved SVR with no adverse effects.[28] A Spanish group (2019) used HCV-viremic donors for 4 HCV-naïve recipients, with preoperative glecaprevir-pibrentasvir continued for 8 weeks post-transplant; all recipients achieved SVR12.[23] A Tennessee group (2019) implemented HCV-viremic donors to HCV-naïve recipients as their standard of care, with DAA therapy started after patients tested NAT-positive and a median time to treatment of 76 days post-transplant.[30] All 53 kidney recipients became viremic, with one case of fibrosing cholestatic hepatitis (1.9%) which resolved with therapy.[30] Once treated, all patients successfully resolved their infection.[30] Patients with longer delays to the start of DAA therapy had higher HCV RNA levels, increased liver enzymes, increased

Table 1. HCV-Viremic Kidney Transplant Programs Across Canada.

Program	Donor	Recipient	Protocol
BC Transplant	Standard criteria	Low wait time	Preoperative prophylactic DAA × 8 weeks
University of Alberta	Standard criteria	Low wait time	Monitor and treat with DAA therapy after HCV-viremic
Western University	Standard criteria	All wait list	Monitor and treat with DAA therapy after HCV-viremic
University of Toronto	Clinical trial protocol	Clinical trial protocol	Preoperative prophylactic DAA × 7 days[32]
Transplant Manitoba	Standard criteria	All wait list	Preoperative prophylactic DAA × 8 weeks
Saskatchewan Transplant	Under development	Under development	Prophylactic DAA therapy approved provincially

1. Transplant programs using a protocol with NAT monitoring, followed by DAA therapy after their recipient becomes HCV-viremic, have done so due to limitations of provincial DAA therapy coverage which mandates HCV viremia prior to DAA funding approval.
2. Manitoba and Saskatchewan approved for 12 weeks DAA therapy for HCV viremic kidney transplants.
3. BC and Manitoba are using preoperative prophylactic glecaprevir-pibrentasvir (Mavriet) DAA therapy.

Note. DAA = direct-acting anti-viral agents; NAT = nucleic acid amplification testing; HCV = hepatitis C virus.

post-transplant CMV and BKV viremia, and a higher risk of rejection.[31] Finally, MYTHIC (2020) was a multicenter open-label trial of 30 patients who received glecaprevir-pibrentasvir therapy started within 3 days of HCV viremic kidney transplant and continued for 8 weeks.[26] All patients achieved SVR and no severe adverse events were deemed related to HCV infection or glecaprevir-pibrentasvir therapy.[26] Taken together, these data demonstrate that the best patient outcomes are obtained with prophylactic DAA or DAA therapy initiated shortly after transplant.

Several Canadian kidney transplant programs have established protocols to use HCV-viremic donors for HCV-naïve recipients (Table 1). However, provincial drug programs have historically required evidence of HCV viremia to obtain DAA drug approval, which can lead to significant delays in therapy. Until recently, prophylactic DAA therapy has been unavailable in Canada outside of a clinical trial protocol. Our objective was to develop a clinical protocol for transplant of HCV-viremic kidneys to HCV-naïve recipients using prophylactic glecaprevir-pibrentasvir for 8 weeks as a standard-of-care practice and subsequently evaluate its implementation.

Methods

Study Design

This is a clinical quality improvement initiative and evaluating this program's implementation is critical to understanding the program's safety and effectiveness and help inform future program development to expand access to transplant for Manitobans using complex donors. Therefore, a prospective observational cohort study of incident adult HCV-naïve recipients of an HCV-viremic kidney transplant treated with prophylactic pan-genotypic DAA therapy for 8 weeks will be done in the Transplant Manitoba Adult Kidney Program (ethics submission underway).

Outcomes

Primary outcomes are SVR at 12 weeks post-transplant (defined as HCV NAT negative) and the tolerability of DAA medications. Secondary outcomes within the first year post-transplant are patient and graft survival, graft function, biopsy-proven acute rejection, HCV transmission rate to recipient (defined as HCV NAT positive), and HCV NS5A resistance. Safety outcomes within the first year post-transplant are fibrosing cholestatic hepatitis, fulminant acute hepatitis, primary and secondary DAA treatment failure, HCV transmission to a recipient's partner, elevated liver enzymes ≥2-fold above normal, abnormal international normalized ratio (INR), angioedema, anaphylaxis, cirrhosis, and hepatocellular carcinoma.

Donor Criteria

Donors must be an eligible consented donor with detectable HCV viremia at the time of deceased donor work-up. Inclusion criteria are a standard criteria donor with an optimal KDPI ≤60 and HIV NAT negative. Optimal KDPI is defined as the KDPI calculated for an identical HCV-negative donor and only standard criteria donors with an "optimal kidney donor profile index" (KDPI) ≤60 will be used (https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/). Kidney donor profile index is a composite score that reflects donor quality, including donor age, height, weight, ethnicity, history of hypertension or diabetes, cause of death, kidney function, donor type (neurological determined death or DCD), and hepatitis C status. Kidney donor profile index was derived prior to the DAA era when outcomes with HCV-positive transplants were quite poor, and "optimal KDPI" reflects the excellent outcomes with DAA therapy and does not score hepatitis C positivity in the KDPI. An optimal KDPI ≤60 is equivalent to a standard KDPI 85 for a 52-year-old, 5″9, 180 lbs, multiracial, hypertensive

DCD donor with a serum creatinine 90 μmol/L. This is a conservative approach using only standard criteria donors (optimal KDPI ≤60, standard KDPI ≤85), but if demonstrated to be safe and feasible then extended criteria donors (KDPI > 85) could be considered.

Exclusion criteria are a history of failed DAA therapy, HBV sAg or NAT positive, and a long-anticipated cold ischemic time ≥24 hours. Treatment failure with interferon with or without ribavirin is not an exclusion criterion.

Recipient Criteria

Recipients must be eligible adult (aged ≥18 years) kidney transplant recipients who have provided informed, multistep consent and who have normal liver function (normal INR and bilirubin) and hepatitis B vaccination with protective HBsAb levels. Exclusion criteria are a history of liver disease; evidence of cirrhosis on routine ultrasound (unless excluded by liver biopsy); previous or current HCV or HBV infection; HIV infection; pregnancy, lactation, or unwillingness to use contraception during the first year post-transplant; inability to swallow or tolerate whole tablets; inadequate adherence to therapy (confirmed by the Manitoba Drug Program Information Network [DPIN] and dialysis review); use of any medication that is contraindicated with glecaprevir-pibrentasvir (eg, phenytoin) and that cannot be safely held for the duration of HCV therapy or changed to an alternative agent; and any condition in the opinion of the transplant nephrologist or hepatologist that would pose a risk to the recipient's safe participation, interfere with their ability to adhere with the treatment, or impact the quality or interpretation of the data (eg, safety monitoring). Patients with persistently elevated alanine aminotransferase (ALT) greater than 2-fold the upper limit of normal will be excluded[26] and elevated aspartate aminotransferase (AST) greater than 1- to 2-fold the upper limit of normal reviewed by the hepatologist to determine their eligibility for this program. Isolated elevated gamma-glutamyl transferase (GGT) is not an exclusion criterion. Elevated alkaline phosphatase ($AlkPO_4$) due to ESRD-related bone mineral metabolism is not an exclusion criterion but the hepatologist will exclude a hepatobiliary cause. Panel reactive antibody is not an exclusion criterion given the safety of thymoglobulin induction therapy in HCV-viremic transplants.

Pre-Transplant Preparation: Multistage Education, Pre-Transplant Consent and Assessment

"Top of the list" patients will be screened for eligibility, and individuals will be sent a letter inviting them and their family/caregivers to a virtual education session on additional opportunities for transplant. This virtual group education session will be led by the transplant coordinators and will discuss the risks and benefits of transplant in the context of new therapies for HCV, including the risks and benefits of transplant from an HCV-viremic donor. Individuals who attend and remain interested in the program will be mailed an informed consent form (Online Appendix 1) and information sheet to consider (Online Appendix 2).

Interested individuals will meet with the transplant coordinator, pharmacist, and physician at a clinic visit. At this individualized information session, the risks and benefits of participating will be reviewed in detail including the potential side effects or medication interactions of the DAA medication and risks of receiving an HCV-viremic kidney. If they are still interested in participating, potential recipients will sign the consent form at this session. As this is a clinical program, consent will be done by the transplant nephrologist.

Consented individuals will undergo additional pre-transplant screening to confirm their eligibility, including outpatient consultation with a hepatologist for assessment of liver suitability for an HCV-viremic kidney. Potential recipients will meet with the transplant pharmacist for a detailed review. Glecaprevir-pibrentasvir is a substrate and inhibitor of cytochrome P450 3A4 (CYP3A4), P-glycoprotein, breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B (OATP1B) enzymes. Concomitant therapy with moderate or strong CYP3A4 inducers such as phenytoin, carbamazepine, phenobarbital, rifampin, and St. John's Wort will be avoided. Risk mitigation will be performed as needed, with referral to neurology for consideration of alternative, noninteracting anti-seizure medications such as levetiracetam. Medications and supplements that can be avoided, such as St. John's Wort, will be discontinued. Essential medications that can be switched to a noninteracting alternative will be addressed prior to listing for an HCV-viremic kidney (eg, dabigatran).

Timely Access to DAA Therapy

The transplant social worker routinely meets with all potential recipients to develop a plan for coverage of immunosuppression. A preapproval for Part 3 Exceptional Drug Status (EDS) for DAA therapy will be added to this process. Direct-acting anti-viral agents therapy is covered for Manitobans with chronic HCV infection under Pharmacare Part 3 EDS and Non-Insured Health Benefits (NIHB). To support the program outlined here, we have successfully petitioned for the criteria to be expanded to include HCV-naïve recipients of HCV-viremic kidneys. The Manitoba Pharmacare program is a deductible/co-pay system whereby there is a family income derived deductible until the family maximum is reached unless there is a current disability or social support (Employment and Income Assistance, EIA) designation. In the event a patient is unable to pay for their deductible, compassionate support will be sought through AbbVie Care. Finally, glecaprevir-pibrentasvir has been added to the hospital formulary for this indication to ensure

an adequate hospital supply of glecaprevir-pibrentasvir is available to initiate prophylactic DAA therapy on call to the operation.

Consent at the Time of Transplant

All participants will be consented with exceptional distribution for an HCV-viremic kidney at the time of offer by the transplant nephrologist on call. This exceptional distribution consent is a routine 2-step process, with the verbal assent obtained on the phone when the transplant nephrologist calls with the details of the kidney offer. Exceptional distribution consent is then obtained in-person and documented by the transplant nephrologist on call during admission for transplant.

HCV-Viremic Donor Protocol

Routine deceased donor work-up will be performed, including HCV antibody and quantitative nucleic acid testing. Prior to donation, a serum sample for HCV RNA quantitation and HCV RNA genotyping will be drawn. Kidneys will be allocated using routine Transplant Manitoba kidney allocation rules to pre-consented patients eligible for participation in this program.

HCV-Viremic Transplant Protocol

This program is largely designed from the EXPANDER and MYTHIC protocols.[26,28] We selected pan-genotypic DAA therapy that is safe in renal failure (glecaprevir-pibrentasvir or Mavriet), as HCV genotype results will not be readily available at the time of transplant. Glecaprevir is an NS3/4A protease inhibitor and pibrentasvir is an NS5A inhibitor. The first dose of glecaprevir 300 mg-pibrentasvir 120 mg will be administered orally on call to the operation and then continued daily for 8 weeks. Liver enzymes and function tests will be monitored by the transplant nephrologist and on-call hepatologist throughout their hospitalization (Online Appendix 3—preprinted orders).

Routine kidney transplant care will be performed per clinical protocol, including induction and maintenance immunosuppression. Outpatient hepatology follow-up will occur at 2, 4, 8, and 12 weeks post-transplant to assess side effects, adherence, liver enzymes, bilirubin, albumin, INR, and complete blood count (CBC). Response to therapy will be evaluated by the hepatologist at 12 weeks post-transplant (4 weeks after DAA therapy is completed), 12 weeks post-DAA therapy, and 12 months post-transplant with quantitative serum HCV RNA, liver enzymes, bilirubin, albumin, INR, and CBC. Patients will be discharged from hepatology at 12 months post-transplant if there are no ongoing concerns, with re-referral in the event of HCV NAT recurrence, persistently elevated liver enzymes or reduced liver function.

NS5A resistance-associated substitutions will be evaluated in the event of a treatment failure, with direct reporting to the transplant donor program so other affected recipients can be treated. Follow-up testing for missed donor co-infection will include HBV sAg and NAT testing and HIV Ab and NAT testing at 3 and 12 months post-transplant.

Post-Transplant Management

Increases in immunosuppression for treatment of biopsy-proven rejection may theoretically increase the risk of HCV relapse; therefore, liver enzymes will be followed monthly for 3 months and HCV NAT testing will be performed 3 months after rejection treatment by steroid pulse, thymoglobulin, or both.[20] Tacrolimus levels may be increased by glecaprevir-pibrentasvir, so tacrolimus drug monitoring will be done upon initiation and discontinuation of glecaprevir-pibrentasvir. Other medication interactions that should be avoided include high-dose cyclosporine and certain statin therapies (eg, atorvastatin and simvastatin). In the very unlikely event that the recipient contracts HIV, there are some drug interactions with antiretroviral therapy such as darunavir, cobicistat, atazanavir, and efavirenz. Consultation with the HIV clinic will be undertaken if this occurs.

Potential Risks and Benefits

Survival benefit of transplantation. HCV-viremic donors have an approximately 100% risk of transmission to HCV-naïve recipients when not treated prophylactically. To balance the risks of HCV transmission with the benefits of transplant, the THINKER trial and Spanish group allocated HCV-viremic kidneys to pre-consented individuals with low wait times[23,25] and a low likelihood of otherwise receiving a transplant within 2 years.[23] BC Transplant (personal communication, Dr Matthew Kadatz) and University of Alberta (personal communication, Dr Kevin Wen) are also allocating HCV-viremic kidneys to HCV-naïve recipients with lower dialysis wait times. However, there is clinical equipoise on this issue. The EXPANDER trial used broader recipient criteria (age $\geq$50 years) and no wait time criteria.[28] The Tennessee group[30] and Western University (personal communication, Dr Anthony Jevnikar) offer HCV-viremic kidneys to all eligible waitlisted individuals without any specific recipient age or wait list criteria. Their rationale is that the significant survival benefit of transplant outweighs the risks of receiving an HCV-viremic kidney transplant given the high success rates of DAA therapy. Due to the long wait times to transplant in Manitoba, we will allocate these kidneys to pre-consented top of the list patients using routine allocation criteria.

Risks of HCV and liver complications. In the largest report by the Tennessee group, the risk of fibrosing cholestatic hepatitis was 1.9% (1/53) following HCV-viremic kidney transplant.[30] It is notable that this individual experienced delayed initiation of DAA therapy but subsequently attained SVR and full resolution with DAA therapy.[30] There have been no cases of fibrosing cholestatic hepatitis in individuals

with prophylactic or rapidly instituted DAA therapy. Chronic HCV patients have a <5% risk of initial DAA treatment failure and the majority (approximately 95%) of those who fail first-line therapy respond to second-line therapy. Therefore, it is estimated that <0.25% of chronic HCV patients do not respond to first- or second-line therapies. Of 98 transplant patients who received HCV-viremic kidneys, all achieved SVR, suggesting that the risk of treatment failure in this population is acceptably low.[25,28,30,33] For those that do not respond to HCV DAA therapy, there is a long-term risk of developing cirrhosis (20% of non-responders; estimated 0.05% overall). There is 2% to 4% annual risk of hepatocellular carcinoma in patients who have HCV-related cirrhosis.

Risk of HCV transmission to a partner. The annual risk of sexual transmission between partners is 0.7%.[34-36] To help mitigate this risk, barrier protection with condoms is recommended while on treatment for HCV.

Risks of DAA therapy. Fatigue, headache, and nausea are the most common complaints. There are many drug interactions associated with DAA therapy. Patients will review with the transplant pharmacist before initiating any new medications while on treatment.

Risk of HBV and liver complications. The HBV NAT window period is 20 to 22 days; therefore, it can be challenging to fully exclude HBV co-infection. Infection can be excluded in donors who are HBsAb positive, HBcAb negative, and HBsAg negative (ie, previously immunized). There is a very low risk that a donor who is HBsAb-negative, HBsAg-negative and HBV NAT-negative will be within the window period and therefore carry an infectious risk.

Kidney donors with established HBV exposure (HBcAb positive) are routinely used for transplantation with exceptional distribution consent to recipients with HBV vaccination and protective antibodies.[37] In this setting, the risk of transmission is considered to be <1%. This protocol mandates HBV vaccination with protective antibodies to reduce the already low risk of transmitting HBV. It is notable that of 98 reported kidney transplants from HCV-viremic donors, there were no reports of HBV transmission.[25,28,30,33] In the unlikely event of HBV transmission, the recipient would require lifelong therapy with an antiviral agent such as entecavir or tenofovir.

Risk of HIV transmission. The risk of a NAT window period HIV infection is anticipated to be very low and these kidneys are routinely used for transplantation with exceptional distribution consent.[13,38]

Data Collection

This is a quality improvement project evaluating the safety and feasibility of a clinical protocol implementation; therefore, all data will be collected as standard of care within the Accuro electronic medical record. A subject identification code list will be kept in a locked, secured office at the Transplant Wellness Center. Data will be extracted from Accuro using the subject identification code list for outcomes and safety analysis. Participants will be followed for long-term outcomes until death-censored graft loss or death with a functioning graft.

Data Analysis

JMP software version 15.2.0 (SAS Institute Inc., Cary, NC) will be used for statistical analysis. For categorical data, Fisher's exact test or Pearson's chi-square test will be used to determine counts and percentages. Parametric continuous data will be analyzed by Student's *t* tests. Nonparametric continuous data will be summarized as median (interquartile range, IQR) unless stated otherwise and analyzed by the Wilcoxon rank-sum or Kruskal-Wallis rank-sum tests. A 2-tailed *P*-value <.05 will be considered statistically significant.

Ethical Considerations in Using HCV-Viremic Donors for Transplant

In 2017, the American Society of Transplantation (AST) convened a consensus conference on HCV-viremic donors, and this panel concluded that the efficacy, safety, and tolerability of DAA therapy make transplantation from HCV-viremic donors to HCV-naïve recipients feasible to study.[18] One recommendation was that there should be a multistep consent process with patient education. This expert panel recommended that treatment costs should be included and outcomes monitored.[18]

In developing this program, we determined that the mandatory elements to safely perform kidney transplants from HCV-viremic donors to HCV-naïve recipients in Manitoba requires patient education and a multistep consent process; timely inpatient access and pre-approved Pharmacare or NIHB coverage for DAA therapy; virology support for HCV NAT follow-up in recipients on treatment and timely evaluation for HCV resistant strains; clear patient treatment protocols delineating standardized care pathways; and long-term outcome follow-up (safety, treatment tolerability, graft and patient survival).

Health Canada Regulatory Requirements

Transplant Manitoba is a Health Canada-accredited program and follows its reporting requirements. Exceptional distribution consent for an HCV-viremic donor will be documented as per routine. This exceptional distribution consent details the risks and benefits of kidney transplantation from an HCV-viremic donor by the accepting transplant physician.

Discussion

We present a clinical protocol for transplantation of HCV-viremic kidneys into HCV-naïve recipients using prophylactic pan-genotypic DAA therapy with the goal to expand

access to deceased donor transplant in Manitoba. This quality improvement project incorporates safety and efficacy measurements while addressing ethical and regulatory considerations for these high infectious risk transplants. Development of this protocol required multidisciplinary stakeholder engagement with transplant and general nephrology, hepatology, virology, transplant surgery, donor coordinators, transplant pharmacy, and nursing. We successfully obtained inpatient hospital formulary approval and outpatient provincial (EDS and NIHB) coverage of prophylactic DAA for HCV-viremic transplants; this information may be useful to other provincial organizations seeking to establish an HCV-viremic transplant program.

Our treatment protocol was developed largely based on the EXPANDER and MYTHIC trials. We chose a pan-genotypic DAA, as genotype information will not be routinely available at the time of transplant. We chose glecaprevir-pibrentasvir as it is safe in patients with renal dysfunction, including dialysis, and can be used without dose adjustment in patients with delayed graft function. Feld et al[32] recently published data demonstrating that treatment with as little as 1 week of glecaprevir-pibrentasvir may be effective at preventing HCV transmission in the transplant setting when it is administered with ezetimibe, an HCV entry inhibitor. While these data show promise for reducing the duration and cost of treatment, given that the use of HCV-viremic donors is still an emerging practice, we chose to be more cautious and use a treatment duration of 8 weeks as per the MYTHIC (2020) trial.[26]

We conducted a deceased donor audit to characterize the potential HCV donor pool. Over a 3-year period (July 2016-June 2019), there were 10 potential donors declined based on HCV- antibody positivity and 2 potential donors declined based on active IV drug use. From these 12 potential donors, 8 were standard criteria without acute kidney injury (AKI) and one had a KDPI 12. These potential donors were declined based on history and prior to approaching the family for organ donation. As donor workup was not performed, it is unknown what proportion were HCV non-viremic versus viremic. However, approximately 30% of individuals attain spontaneous clearance of HCV[39]; therefore, we estimate approximately 2 non-viremic and 6 HCV viremic standard criteria potential donors. After donor consent and evaluation, we estimate approximately 1 to 2 HCV viremic donors/year or 2 to 4 HCV viremic kidney transplants/year in Manitoba.

Key Findings

This program successfully advocated for and obtained hospital formulary, provincial EDS, and NIHB to provide prophylactic DAA therapy for this indication. This information may be useful to other provincial transplant organizations seeking to establish an HCV-viremic kidney transplant program with prophylactic DAA drug coverage.

Limitations

The major limitation was that patient engagement was not undertaken during the program development process. However, Transplant Manitoba routinely collects a locally developed patient-reported experience measure (PREM) in all newly transplanted patients (Online Appendix 4) and additional PREMs and patient-reported outcome measures are under consideration. This includes patients who will participate in this HCV-viremic kidney transplant program. These data will be used in an iterative fashion to modify the program as needed for optimal patient outcomes and experiences. Another limitation is the low anticipated numbers of HCV-viremic kidney transplants that are anticipated to occur in Manitoba which will limit power to detect safety and efficacy.

Implications

The goal of this quality improvement project is to improve access to kidney transplantation for Manitobans. We hope this clinical protocol will be useful to other transplant groups in establishing programs for these low frequency, high infectious risk transplants, such as patient information sheets and consent forms. It would be helpful to establish common data elements across provincial transplant programs to evaluate the safety and efficacy of this approach on a national basis. Finally, we anticipate this will be a safe and effective way to expand access to kidney transplant from a previously unutilized donor pool.

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Ethics approval

Protocol submitted for institutional ethics approval.

Consent for publication

All authors consent for publication

Availability of Data and Materials

Appendix 1 - Informed consent form
Appendix 2 - Patient information sheet
Appendix 3 - Preprinted inpatient orders
Appendix 4 - Patient reported experience measure

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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