Fenofibrate to prevent Ischemic Cholangiopathy in Donation after Circulatory Death liver transplantation (FICsDCD)

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MEGA Award Protocol

Title of the study:	**Fenofibrate to prevent Ischemic Cholangiopathy in Donation after Circulatory Death liver transplantation (FICsDCD)**
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Abstract

Ischemic cholangiopathy (IC) is an early-onset, progressive bile duct stricturing syndrome occuring in 5-15% of transplanted livers, leading to biliary obstruction and allograft failure in upto 60% of cases. There is no definitive treatment for IC besides re-transplantation. The differential rate of IC drives the global preference for livers donated after brain death, over more abundant livers donated after circulatory death (DCD) that are prone to warm ischemia—the primary precipitant of IC. Any intervention to ameliorate IC will likely improve DCD organ utilization globally, thereby reducing transplant waitlist mortality and morbidity. Toxic bile acids (BA) in stagnant bile cause bile duct injury and stricturing, which may explain why stricturing progresses even after ischemia resolves at transplantation. Peroxisome proliferator-activated receptor (PPAR) agonists (such as the generic oral agent **fenofibrate**) potently down-regulate BA synthesis, promote BA excretion, and are safe and effective in other cholestatic diseases, but are not studied in transplant recipients. We hypothesize that fenofibrate could be safe, effective, cheap, and thus generalizable to impede the IC propagation. **In this prospective pilot study, we aim to evaluate 1) the tolerability and safety, 2) the efficacy of 12 weeks once-daily fenofibrate in reducing IC incidence after DCD liver transplantation, 3) assess the association between serum markers of cholestasis and development of IC.** Tolerability and safety will be assessed as proportions of: drug discontinuation, and new grade 3 or 4 adverse events. Efficacy will be assessed as incidence of cholangiographically-diagnosed IC and incidence of any IC-related complication.

Research Plan

Specific Aims

Specific Aim 1: To assess the tolerability and safety of 12 weeks once-daily fenofibrate (Lofibra) in a LT recipient population

Primary endpoint: Proportion of patients discontinuing fenofibrate due to adverse events

Secondary endpoints:

a. Proportion of patients with a new grade 3 or 4 adverse event.

b. Proportion of patients with acute cellular rejection during fenofibrate treatment

c. Mean change in calculated glomerular filtration rate (eGFR) from baseline during fenofibrate treatment weeks 4, 8, 12, and at 4 weeks after end of treatment

d. Proportion of patients with myopathy confirmed by serum creatine kinase elevation at weeks 4, 8, 12, and at 4 weeks after end of treatment

Specific Aim 2: To assess IC incidence after 12 weeks of once-daily fenofibrate (Lofibra) in DCD LT recipients, compared with a historical, untreated control. Treatment and control populations will have an elevated predicted risk of IC, defined as alkaline phosphatase >2.5x upper limit of normal (ULN) at 21-60 days after LT.
Primary endpoint: IC incidence with 12 weeks fenofibrate versus a historical untreated cohort.
Secondary endpoints:
a. Incidence of any IC-related complication at 12 weeks of fenofibrate treatment as a composite endpoint: biliary intervention (biliary stricture dilation, endoscopic biliary stent placement, percutaneous biliary drain placement), initiation of antimicrobial therapy for cholangitis or biloma, re-transplant evaluation due to IC, or death attributed to IC.
b. Rate of alkaline phosphatase improvement to <1.67x ULN after 12 weeks fenofibrate.

Specific Aim 3: To assess the association between serum biomarkers and IC development.
Endpoints: Correlation of serum alkaline phosphatase, gamma glutamyl transferase, bile acids, fibroblast growth factor 19 (FGF19) and 7-alpha-hydroxy-4-cholesten-3-one (7AC4) levels at weeks 0, 4, 8, and 12 of treatment, with development of IC at 12 weeks of treatment.

II. Background and Significance

Liver allografts donated after circulatory death (DCD) improve access to liver transplantation (LT) by increasing organ supply. Widespread adoption DCD LT however is hindered by the higher risk of ischemic cholangiopathy (IC) in DCD organs, a progressive biliary structuring syndrome observed within weeks-to-months after LT, which increases morbidity, mortality, and cost by demanding frequent cross-sectional imaging, endoscopic and percutaneous biliary intervention, hospitalization, parenteral antimicrobials, and in almost 60% of individuals, re-transplantation due to allograft failure.[1] Elevated alkaline phosphatase (ALP) at 1 and 2 months are validated early signals of impending IC, but lack of preventative interventions relegate LT centers to manage complications reactively when they arise.[2]

Rates of IC in livers procured after brain death (DBD) range 1-10%, while DCD IC rates range 10-30%.[3–5] DCD IC rates are better at experienced centers, with Mayo Clinic Arizona (MCA) and Mayo Clinic Florida (MCF), two of the largest DCD LT centers in the US—having a rate of 10-12% (N=20-24/year).[1] Despite this, the risk of DCD IC dissuades most LT centers from entertaining DCD organs. Almost 30% of recovered DCD livers are unused, compared to 7.5% of DBD livers, and despite their greater abundance, DCD livers account for just 8.5% of the transplanted livers in the United States.[6] Effective interventions against IC may therefore increase DCD liver utilization.

The key histologic features of early IC are biliary endothelial ischemic necrosis and consequent impairment of biliary drainage (choleresis).[3,5] The duration of liver non-perfusion after donor cardiac standstill (warm ischemia) is the most important risk factor for IC that explains the higher rate of IC in DCD versus DBD livers, with warm ischemia >30 minutes being a standard cutoff for rejecting an allograft offer.[7] However, warm ischemia time does not explain the often inexorable progression of biliary destruction well after arterial perfusion is re-established at transplantation. This suggests other ongoing injury processes in the transplanted liver, intervening on which could mitigate the downstream complications of IC.

An attractive hypothesis for post-transplant IC progression is the accumulation of bile acids (BA)— hydrophobic molecules with detergent and apoptotic effects on hepatocyte and cholangiocyte lipid membranes—within the biliary tree.[3,8] The pathologic effects of BA are recognized to the extent that flushing the biliary tree to remove BA is standard at time of organ procurement. The immediate post-transplant period is also marked by low concentrations of bile

phospholipids which impairs BA micellization, and low concentrations of bicarbonate which impairs bile alkalinization, both of which likely potentiate BA-induced cytotoxicity.[3] While the antecedent to IC is impaired choleresis due to bile duct necrosis, it is conceivable that BA stasis propagates injury and/or impairs healing after transplantation. The hypothesized process is therefore a spiral of BA accumulation due to ischemia-induced biliary injury, unopposed BA activity due to lower phospholipid and bicarbonate concentrations, BA-induced cytotoxicity, cytotoxicity-induced biliary injury, and further BA accumulation.

Countering the deleterious effects of BA in IC could draw parallels from the treatment of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), both of which involve disrupted choleresis and accumulated toxic concentrations of BA. Importantly, unlike PSC and PBC where disease progression is fueled by immune activity, the injury trigger in IC appears to be self-limited; ischemia prior to transplantation. It is reasonable therefore to postulate that pharmacologically reducing BA concentrations in a DCD allograft, beginning soon after transplantation, could impede biliary injury and improve allograft survival.

The peroxisome proliferator-activated receptor (PPAR) agonists bezafibrate and fenofibrate (fibrates), which potently downregulate BA synthesis, activity, and promote choleresis, are promising therapeutics for PBC and PSC.[9,10] At least 11 prospective trials (including one pivotal trial) in PBC (N=481), and 2 prospective trials in PSC (N=23) have demonstrated their ability to improve ALP, BA, and other disease endpoints over the standard of care.[11]

While approved for dyslipidemia and used off-label for pre-LT PBC and PSC, fibrate safety or efficacy have not been studied in any transplant population for any indication. Additionally, despite the likely benefits (including cost of $5-25/month), the known risk profile of fibrates, including nephrotoxicity, hepatotoxicity, and myotoxicity, require study in LT recipients who are prone to these toxicities from immunosuppressives and/or their baseline clinical state.

In this prospective pilot study, our primary aim is to describe the tolerability and safety of 12 weeks of once-daily fenofibrate in a LT population, with efficacy as a secondary aim, and determining associations of cholestasis and bile acid activity biomarkers with IC as a tertiary aim.

We believe this pilot study to have at least four key implications on current post-LT care or in opening new areas of investigation. First, demonstrating fenofibrate tolerability and safety early after LT is useful context of IC but also because both PBC and PSC have a 20% recurrence rate after LT and fenofibrate may be considered for post-LT prophylaxis (current standard of care is universal lifelong ursodeoxycholic acid after LT for PBC, and observation alone after LT for PSC). Second, if an efficacy signal is demonstrated, we will leverage the existing three-site Mayo Clinic collaboration (together the largest transplant consortium by far) to conduct a randomized controlled trial to more conclusively assess efficacy of fenofibrate in preventing IC. Third, we hope to determine if biomarkers besides ALP—a test confounded by other liver processes—are associated with IC and facilitate early detection. Fourth, data gathered may allow us to investigate a predictive scoring model utilizing donor and patient characteristics and these biomarkers.

III. Progress Report and Preliminary Studies

As two of the largest DCD LT program in the nation, the MCA and MCF transplant hepatology teams including this study's PI and Co-Is are experienced in diagnosing and managing IC. Our group holds a monthly DCD IC Multidisciplinary Conference to review cases and discuss management. Finally, the MCA LT Program has contributed to seminal peer-reviewed papers on the DCD IC syndrome including the recently proposed IC classification system.[1] At present we are developing a dataset of over 300 DCD LT recipients at our center which will be used to identify the historical controls of this study.

IV. Research Design and Methods

Study design: A single-arm, open-label, prospective study of 12 weeks of fenofibrate (Lofibra) 160mg once daily in donation after circulatory death liver transplant recipients who have serum alkaline phosphatase >2.5x ULN 21-60 days after transplantation, to determine fenofibrate tolerability, safety, and efficacy in preventing the ischemic cholangiopathy.

Treatment cohort: Recipients of DCD liver transplants at MCA or MCF

Historical cohort: DCD liver transplant recipients at MCA or MCF between 1/1/2016-6/1/2021

Diagnosis of IC: We will utilize previously-published diagnostic criteria for IC, defined as the occurrence of non-anastomotic biliary strictures in the absence of hepatic artery compromise[1]

Inclusion criteria:

1. Female or male patients who have undergone DCD LT
2. At least one serum ALP level >2.5x ULN between post-LT days 21-60 days (inclusive) after LT.

Exclusion criteria:

1. LT performed for primary sclerosing cholangitis or primary biliary cholangitis
2. Hepatic artery compromise (e.g thrombosis, stenosis), evaluated on abdominal doppler ultrasonography or angiography prior to enrollment..
3. Untreated biliary anastomotic (surgical) stricture or bile leak between days 0-60 after LT, evaluated during routine clinic examinations, labs, and abdominal ultrasonography.
4. Baseline GFR <30 ml/min
5. Previously known intolerance or allergy to fenofibrate
6. Other clinically significant comorbid condition, including psychiatric conditions, which in the opinion of the study team, may interfere with patient treatment, safety, assessment, or compliance with the treatment
7. Adults lacking capacity to consent to treatment

Interventions:

1. Consenting eligible patients will receive the fenofibrate formulation *Lofibra*, 160mg or renally-adjusted equivalent daily. Intended treatment duration of 12 weeks.
2. Post-transplant laboratory monitoring will be per standard Institutional protocol, at least weekly, through treatment period. Study laboratory monitoring will be done as below.

Analyses:

Specific Aim1:

a. Tolerability: Proportion of patients who discontinue fenofibrate due to adverse event.
b. Safety:
- Proportion of patients with a new grade 3 or 4 adverse events based on CTCAE 5.0 Scale

- Proportion of patients with acute cellular rejection during fenofibrate treatment
- Mean change in eGFR from baseline at treatment weeks 4, 8, 12, and post-treatment week 4
- Proportion of patients with elevated serum CK at weeks 4, 8, 12, and post-treatment week 4

Specific Aim 2:
a. Efficacy: We will use a two-group design to test whether Group 1 (treatment) proportion (P1) is different from Group 2 (control) proportion (P2) (H0: P1-P2=0 versus H1: P1-P2≠0). We will use a two-sided, two-sample Fisher's Exact Test with Type I error rate (α) of 0.05.
b. Sample size: Allowing a 10% dropout rate, a sample size of 32 in the treatment arm and 116 in the historical control arm (1:4 ratio) will achieve 80% power to detect an IC proportion reduction of 30% in the control arm to 5% in the treatment arm.

Specific Aim 3: Serum biomarker association with IC development: We will use the Wilcoxon Rank-Sum test to compare serum ALP, gamma glutamyl transferase, serum BA, FGF19 and 7AC4 levels at weeks 0, 4, 8, and 12 of treatment, with development of IC at 12 of treatment.

Data management: The study will use REDCap, a secure web platform for building and managing online databases and surveys for electronic data collection. REDCap provides automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, branching logic, file uploading, and calculated fields.

Schedule of Events

Procedure	Screening: Post-LT day 21-60	Treatment			Post Treatment
		Weeks 0-4	Weeks 5-8	Weeks 9-12	Week 4
Informed consent	X				
Inclusion and exclusion criteria	X				
Physical examination	X				
Medical history	X				
Intervention: fenofibrate		Daily	Daily	Daily	
Routine Labs*	X	Weekly	Weekly	Weekly	Weekly
Study Labs**	X	Once[a,b]	Week 6[b]	Week 12 [b]	Once [b]
Lab result review		Weekly	Weekly	Weekly	Once
Assess tolerability, safety		Weekly	Once	Once	Once

*Protocol transplant monitoring labs (billed to insurance): total bilirubin, ALP, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, creatinine, eGFR, and complete blood count.
**Study labs per FICsDCD budget: GGT, serum bile acids, CK, FGF19 (ELISA), 7AC4 (LC-MS)
[a] collect within 3 days after start of treatment
[b] combine with transplant monitoring labs

Study Strengths and Limitations:
The mechanisms of action of PPAR-alpha agonists like fenofibrate predict a strong likelihood of impeding the dreaded transplant complication of IC, yet has not been studied. We propose the first safety and tolerability analysis of fenofibrate in LT recipients. Additionally, we assess the efficacy in reducing IC incidence in a population at increased risk of IC (based on elevated alkaline phosphatase levels at 3-5 weeks after transplant). We proposed fenofibrate as it is readily available and the cheapest PPAR-alpha formulation, at $5-25/month. Finally, MCA and MCF, as two of the largest DCD LT centers in the nation, makes us uniquely positioned perform this study, and our existing IC study collaborations in Minnesota and Florida may allow a future multi-center

randomized controlled trial to more conclusively assess efficacy. Our proposed pilot study is primarily limited by its sample size, owing to a low anticipated IC accrual rate, and the consequent inability to randomize a prospective control arm.

Study Timeline:

Month	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18
Enrolment	X	X	X	X	X				
Treatment	X	X	X	X	X	X	X		
Develop Historical Cohort								X	
Analysis								X	X

V. Human Subjects

Population: The treatment-arm population is 32 adults with decision making capacity, and enrolled from among the MCA and MCF LT recipient population. The control arm is a historical LT recipient population. The study does not involve fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable.

Research Materials: We will collect, analyze, and biobank blood for study purposes in 32 participants. Participants will receive telephone contact from study coordinators at least monthly during 3 months of treatment, and 1 month after treatment. We will review the electronic medical record of the 32 participants and 116 historical controls including clinical notes, laboratory, imaging, and pathology results, and procedure reports.

Enrolment strategy: Patients who have undergone DCD LT will be screened for eligibility between days 21-60 days after LT. All consecutive LT recipients meeting criteria will be offered enrollment in the study. The historical control cohort will be identified through the Mayo Clinic electronic medical record.

Potential Risks: Fenofibrate has been FDA-approved for dyslipidemia since 2004. The most common serious adverse events (SAEs) reported are elevated liver enzymes (3-13%), headache (3%), abdominal pain (5%), constipation (2%), nausea (2%), back pain (3%), CK elevation (3), and respiratory symptoms (2-6%). Fibrates are also associated with elevated serum creatinine, an important consideration in LT recipients who are concurrently exposed to other nephrotoxic agents and/or may have baseline renal impairment. In a large meta-analysis, mean creatinine increase was 0.37mg/dl, and GFR impact was minimal (2.7 ml/min). Moreover, both returned to baseline after drug cessation.[12] Fibrates are postulated to increase creatinine production, with direct nephrotoxicity occurring to a lesser degree. We will monitor participants with weekly labs and monthly and ad hoc study coordinator calls to determine SAEs. Patient reported intolerance or grade ≥3 SAEs (CTCAE 5.0 Scale) attributed to drug will be addressed with temporary or permanent drug discontinuation or dose reduction.

Protection: The primary aim of this study is to determine if the widely-used medication fenofibrate is tolerable and safe after LT, a unique population in which it has not been studied. Particular areas of interest are nephrotoxicity, hepatotoxicity, myotoxicity, and risk of allograft rejection. We use the standard, CTCAE 5.0 scale to determine severity of adverse events. The baseline safety and tolerability profile of fenofibrate is obtained from the FDA and post-marketing ('real world') data reported through LexiComp. As we are intervening early after transplantation, participants will be monitored intensively by the Transplant Program (twice weekly labs and at least twice-weekly transplant coordinator contact) in addition to Study staff.

Benefits: IC is among the most serious complications after LT. The proposed study of fenofibrate, a medication generally considered safe albeit not studied in a LT population, may facilitate further study of this agent as a low risk, low cost, intervention to impede the development of IC and its downstream complications including frequent biliary intervention, hospitalization, loss of functional capacity, allograft failure, and need for re-transplantation.

VI. Gender/Minority Mix There are no known gender or racial disparities in IC. All eligible, consecutive LT recipients irrespective of gender or race will be offered study enrolment.

VII. References:

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