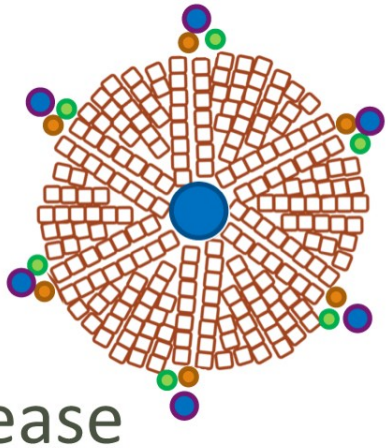
CaNAL

Canadian Network for Autoimmune Liver disease



Clinical Study Protocol

CaNAL Registry

Version 2.0: 27 September 2017

Confidential

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Study Initiator/Sponsor: Canadian Network for Autoimmune Liver disease

Protocol Synopsis

Name of Sponsor: The Canadian Liver Foundation

Title of Study: Canadian Network for Autoimmune Liver disease – CaNAL

First Objective: To develop a Canadian registry of PBC and AIH patients allowing retrospective and prospective long-term follow-up of patient visits, interventions and clinical events.

Second Objectives:
- To compare of FibroScan staging with Global score and UK-PBC risk score to prognosticate clinical endpoints of end stage liver disease.
- To investigate the clinical variants of PBC with attention to ductopenic variant and autoimmune hepatitis overlap syndromes.
- To determine geo-epidemiological differences in phenotypes in relation to gender/race/ethnicity and clustering of PBC and AIH in aboriginal populations.
- To analyze biochemical markers and other factors indicative of early recurrence of PBC and AIH following liver transplantation.

Exploratory Objective: To study changes in quality of life during prospective long-term follow-up. To study and develop a sharper definition of PBC + AIH overlap.

Methodology: The study design is a longitudinal multi-center observational cohort study. Retrospectively and prospectively acquired data will be collected from major Canadian sites. At each site the investigator will identify all consecutive PBC and AIH patients from existing clinical databases and at the outpatient clinic. Follow-up data on these patients will be obtained from databases, patient files and digital hospital information systems. Patient data will be anonymized.

Number of Patients (planned): 1500 - 2000 patients

Study Population: All patients diagnosed with PBC, AIH and PBC+AIH

Inclusion Criteria: Patients with diagnosis of PBC, AIH or PBC+AIH overlap, age at diagnosis >18 years

Exclusion Criteria: None

Duration of Study: Inclusion 2017 – 2020, follow-up to 2025 with possibility to expand

Outcome Measure: Response to therapy, FibroScan, end stage-liver disease, quality of life

Statistical Methods: Sample size justification: With 1500-2000 patients a wide spectrum of PBC and AIH patients is collected, allowing detailed analysis of the different endpoints. For the endpoint clinical progression, it is expected that 30 - 40% will reach this within 10 years of follow-up ~ 450-600 events. This ensures a reasonable power to study at least 20 variables while adjusting for center heterogeneity.

The following abbreviations and specialist terms are used in this report.

Abbreviation	Definition
AIH	Auto Immune Hepatitis
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
EOS	End of Study
GGT	Gamma-Glutamyl Transferase
MELD	Model for End Stage Liver Disease
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
OCA	Obeticholic Acid
PBC	Primary Biliary Cholangitis
PK	Pharmacokinetic
PSC	Primary Sclerosing Cholangitis
SE	Standard Error
SD	Standard Deviation
UDCA	Ursodeoxycholic Acid

CONTENTS

Summary protocol

1. Background

Primary biliary cholangitis (PBC) is a progressive hepatobiliary disease characterized by a non-suppurative cholangitis and granulomatous destruction of 30 to 80 μm interlobular bile ducts.[1, 2] The progressive ductopenia leads to accumulation of bile within the liver resulting in fibrosis. The standard of care for PBC is ursodeoxycholic acid (UDCA) therapy,[3-8] with the opportunity of obeticholic acid therapy for non-responders in the USA. Approximately half of PBC patients develop cirrhosis and those with progressive disease accounts for up to 10% of patients requiring liver transplantation in Canada.[1, 9] There is an unmet need for up to 50% of PBC patients, who require adjunctive therapies to UDCA. Large consortia have recently proposed biochemical and clinical algorithms to determine those at risk for disease progression.[10, 11] However, further validation by elastography, additional prognostic biomarkers and other refinements are required to better understand and predict patients at risk and in need of further therapy.

PBC is considered an autoimmune disease because ~ 85% of PBC patients make anti-mitochondrial antibodies. Up to 30% of patients with autoimmune hepatitis (AIH) also make anti-mitochondrial antibodies and an overlap syndrome of two disorders has been recognized.[12, 13] While immunosuppressive therapy has proven life saving in patients with AIH, the role that autoimmunity plays in causing bile duct damage in patients with PBC is unknown. Immunosuppression is of limited utility for PBC patients [14] and liver transplant recipients on more potent immunosuppressive regimens develop earlier and more severe recurrent PBC.[15, 16] Other adjunctive therapy for UDCA non-responders has been targeted to genetic and environmental factors associated with PBC.[1, 17] An increased prevalence occurs in family members (1% to 7%) and PBC is more frequently observed in monozygotic vs. dizygotic twins.[18, 19] There is also a markedly increased prevalence of disease in First Nation Canadians where PBC has the characteristics of an autosomal recessive disease in some extended families.[20, 21] Several case control and genome wide association studies have linked the HLA class II, the IL-12 cytokine axis and other innate immunoregulatory genes. A proof of principal trial using ustekinumab was discontinued due to lack of efficacy, however.[22, 23]

Spouses, unrelated family members and care providers can develop PBC, implicating environmental factors in the disease.[24, 25] PBC clusters geographically in regions[26, 27] and migration studies show that children develop the relative incidence of their adopted host country.[28, 29] An infectious disease process is suggested by observations from liver transplantation as more potent immunosuppressive regimens using tacrolimus accelerate the onset and severity of recurrent disease as compared to the less potent cyclosporine A (CsA).[9] [30, 31] A human betaretrovirus has been characterized in PBC patients [32] and combination anti-retroviral therapy has shown utility in improvement hepatic biochemistry and histology, while reducing viral load.[33]

Other adjunctive therapies to UDCA have been directed towards improving cholestasis. Controlled trials have shown significant biochemical improvement in PBC patients treated with obeticholic acid - a bile salt with

FXR agonist activity.[34, 35] Nevertheless, a better understanding of the natural history of PBC, biomarkers predictive of disease progression, and non-response to therapy as well as better knowledge of the etiology and pathogenesis of PBC are required. The Canadian Network of Autoimmune Liver Disease (CaNAL) is well poised to conduct the proposed studies as team members have participated in Global PBC consortia [10, 36, 37] as well as cross Canada collaborative GWAS,[38-42] liver transplantation, [9, 43-46] other PBC and AIH related studies.[47-49]

2. Objectives

1. To develop a Canadian registry of PBC and AIH patients allowing retrospective and prospective long-term follow-up of patient visits, interventions and clinical events.
2. To compare of FibroScan staging with Global PBC score and UK-PBC risk score to prognosticate clinical endpoints of end stage liver disease.
3. To investigate the clinical variants of PBC with attention to ductopenic variant and autoimmune hepatitis overlap syndromes.
4. To determine geo-epidemiological differences in phenotypes in relation to gender/race/ethnicity and clustering of PBC and AIH in aboriginal populations.
5. To analyze biochemical markers and other factors indicative of early recurrence of PBC and AIH following liver transplantation.

3. Study Methodology

3.1 Study Design

Retrospectively and prospectively acquired data will be collected from major Canadian centers to include all the liver transplantation programs. The predicted size of the resulting study population will be 1,500-2,000 subjects.

This study is a longitudinal observational cohort study of patients diagnosed with PBC, AIH or PBC&AIH overlap. The CaNAL clinical research core is the creation of a nationwide registry and network focusing on high quality long-term follow-up of individual patient data from major Canadian centers.

CaNAL will collect both retrospective and prospective data: The investigators will identify all consecutive PBC and AIH patients from databases of previous studies and at the outpatient clinic. Follow-up data on these patients will be obtained from databases, patient files and digital hospital information systems. Overall 3 types

of data capture are identified depending on date of diagnosis and follow-up (Figure 1):

1. CaNAL will collect prospective data from patients already diagnosed with PBC and AIH along with their historic data; i.e a retrospective capture of diagnosis and clinical follow-up visits until today (type 1)
2. CaNAL will collect prospective data of newly diagnosed patients (type 2)
3. CaNAL will collect retrospective data of patients diagnosed with PBC or AIH who have experienced a clinical event (liver transplantation / death) or are lost to follow-up (type 3)

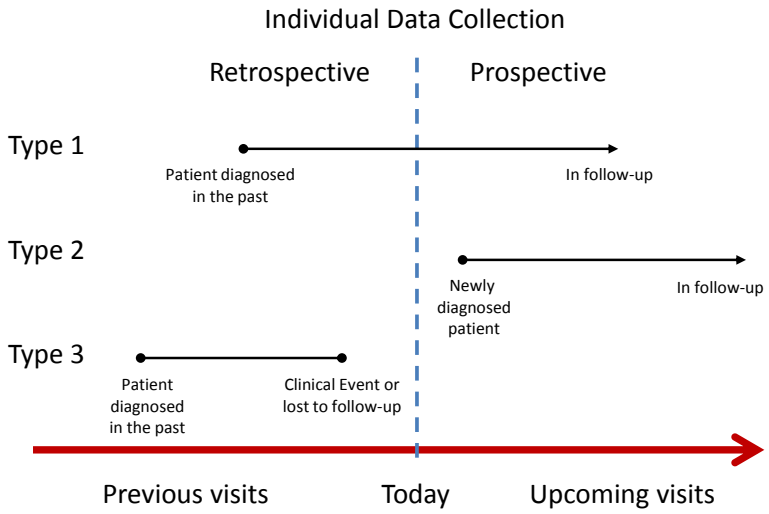

Figure 1. *Retrospective and prospective data collection of follow-up visits for individual patients: already in follow-up (type 1), newly diagnosed (type 2) and patients identified in the past with an event or lost-to follow-up (type 3).*

3.2 Patient Population

All patients with an established diagnosis of PBC or AIH in accordance with internationally accepted guidelines.

3.3 Data Collection

Retrospectively and prospectively acquired data will be collected from major Canadian sites. The predicted size of the resulting study population will be minimum 1,500-2,000 subjects. At each site the investigator will identify all consecutive PBC and AIH patients from existing clinical databases and at the outpatient clinic. Follow-up data on these patients will be obtained from databases, patient files and digital hospital information systems. Patient data will be anonymized. A standardized electronic case record (e-CRF) form will be used to capture the data. The e-CRF form has been designed in REDCap, a secure web based application supporting data capture for research studies. REDCap is designed to comply with HIPAA security regulations. The CaNAL

REDCap database (REDCap project CaNAL) has been established at the University of Alberta under the jurisdiction of WCHRI.

Each centre will have data collectors to import/insert their own patient data in into the REDCap database. The data collectors will be trained at individual sites and only authorized study staff will have access to REDCap. It is likely that most centres will employ their own data collectors. Should data collectors travel to sites outside their own, they will be trained appropriately at the remote sites to upload the requisite data into the REDCap database.

All study participants will be given a unique CaNAL participant number (study number).

Individual centres will have access only to their own data and patient identifiers will only be visible to the individual centres. The steering committee will have access to all anonymized data within the REDCap database, that is without any patient identifiers.

Participation in this study is voluntary. The participant may at any time decide to consent to be in this study. Their continuing medical care will not be affected.

A subset of patients will be invited to participate in quality of life assessment during their regular visit to the clinic (time for filling in the forms 20-30 min).

The following data will be collected:

- Demographics and lifestyle: age, sex, ethnicity, place of birth, smoking and drinking habits, drugs, pregnancy and parity, education and occupation, living status, environmental exposure and family history of PBC and AIH
- Date of diagnosis, other major diseases affecting 5-year life expectancy
- Treatment, dose and duration of treatment
- Pre- and post- treatment serum biochemical parameters: ALP, total bilirubin, albumin, gamma-GTP, AST, ALT at each visit until end of follow-up
- Biopsy, US, MRI or FibroScan values measuring severity of liver disease: stage of fibrosis/steatosis, cirrhosis, HCC
- Date and events: Liver transplantation, death, cause of death, HCC, ascites and variceal bleeding
- Post Liver transplantation data on recurrence of disease
- Prospective Quality of life assessment will be collected for a subset of patients

3.4 Statistics

3.4.1 Sample Size Justification

To be able to study multiple endpoints (death, liver transplantation, decompensation, HCC, change in FibroScan and fibrosis parameters) and multiple effects of patient characteristics (age, sex, race), different treatments (UDCA, OCA, fibrates and others) potential changes in biomarkers (bilirubin, ALP, AST, ALT, albumin, platelets, GGT, IGM, IGG, ...) a minimum of 2000 patients are required with 5-year event rate of 10-30 % to achieve a reasonable power of 80%.

3.4.2 Statistical Analysis

Analysis will be both cross sectional and dependent on follow-up time in nature. A range of analytic methods will be applied as appropriate depending on aims, endpoints and outcomes.

For the endpoints decompensation, HCC, liver transplantation and death, survival analysis techniques including dynamic survival analysis, multistage modelling and competing risks methods will be used. Of special interest are the following factors:

1. The potential added effect of repeated FibroScan measurements to identify patients at high risk of an event

2. The difference in outcome between different etiologies and

3. The possible effect of new markers (genetic and environmental)

Cox regression analysis will be applied where needed and will be stratified by center, state to account for heterogeneity between centers. The multivariate models will adjust for calendar time of diagnosis, sex, age and the GLOBE or UK risk score.

For the endpoint response to therapy logistic regression techniques will be applied.

For the behavioral patterns of biochemical values over time repeated measurement techniques will be applied.

For the analysis of quality of life over time repeated measurement techniques will be applied.

4. Confidentiality and Publication

The Consortium Agreement PUBLICATION and AUTHORSHIP RULES of the CaNAL Consortium (appendix) applies. The study protocol and completed case record forms are property of the CaNAL Consortium. The results of the study will be published in the international literature. All investigators have the opportunity to do ancillary studies as described in Consortium Agreement PUBLICATION and AUTHORSHIP RULES of CaNAL (appendix). The steering committee will steer the Network. Proposals are separated into projects including all sites and individual study proposals including specific sites of participating centers.

5. Time Schedule

Identification principal investigators/steering committee: January 2016

Synopsis Protocol completion: March 2016

Launching CaNAL: March 2017

Design e-CRF in REDCap: March-October 2017

REB approval: February-December (site specific) 2017

Assembly of preliminary database: November 2017 – February 2018

Start of data collection: November 2017

6. Ethics and Legal Aspects

This study will be performed in accordance with the protocol, the principles of the Declaration of Helsinki 1964 as modified by the 59th WMA General Assembly, Seoul, South Korea October 2008 and the local national laws governing the conduct of clinical research studies.

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