ABSTRACT
Autoimmune liver disease (AILD) spans a spectrum of chronic disorders affecting the liver parenchyma and biliary system. Three main categories of AILD are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). This review condenses the presentation and discussions of the Single Topic Conference (STC) on AILD that was held in Ottawa, Ontario, in November 2019. We cover generalities regarding disease presentation and clinical diagnosis; mechanistic themes; treatment paradigms; clinical trials, including approaches and challenges to new therapies; and looking beyond traditional disease boundaries. Although these diseases are considered autoimmune, the etiology and role of environmental triggers are poorly understood. AILDs are progressive and chronic conditions that affect survival and quality of life. Advances have been made in PBC treatment because second-line treatments are now available (obeticholic acid, bezafibrate); however, a significant proportion still present suboptimal response. AIH treatment has remained unchanged for several decades, and data suggest that fewer than 50% of patients achieve a complete response and as many as 80% develop treatment-related side effects. B-cell depletion therapy to treat AIH is in an early stage of development and has shown promising results. An effective treatment for PSC is urgently needed. Liver transplant remains the best option for patients who develop decompensated cirrhosis or hepatocellular carcinoma within specific criteria, but recurrent AILD might occur. Continued efforts are warranted to develop networks for AILD aimed at assessing geo-epidemiological, clinical, and biochemical differences to capture the new treatment era in Canada.

KEYWORDS: autoimmune hepatitis; cirrhosis; overlap syndrome; primary biliary cirrhosis; primary sclerosing cholangitis.
INTRODUCTION

The Single Topic Conference (STC) on Autoimmune Liver Disease (AILD) from the Canadian Association for the Study of the Liver (CASL) initiated a series of sessions in November 2019 to address new concepts in (1) disease presentation and clinical diagnosis; (2) mechanistic themes in AILD; (3) treatment paradigms; (4) clinical trials, including approaches and challenges to new therapies; and (5) looking beyond traditional disease boundaries.

This review condenses the presentation and discussions of the STC in AILD that was held in Ottawa, Ontario, in November 2019.

Session 1: Disease Presentation and Clinical Diagnosis

CURRENT STATUS OF THE EPIDEMIOLOGY OF AILD

The three major categories of AILD are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Overall, autoimmune diseases affect women more than men, with ratios ranging between 4:1 and 6:1, and the incidence of autoimmunity seems to be rising worldwide.

The overall prevalence of AIH ranges from 15 to 25 cases per 100,000 inhabitants in Europe and is increasing among both women and men (1). The incidence of AIH among patients aged younger than 18 years in Canada was estimated to be 0.23 per 100,000 children (2). AIH occurs in all ethnic groups and in all age groups. Bimodal distribution has been suggested, with peaks around puberty and between the fourth and sixth decade (1). In Sweden, the bimodal distribution of AIH is seen only among females (3); however, no bimodal distribution was observed in South Korea when the average annual sex-adjusted incidence rate per 100,000 population and incident cases (2009–2013) were taken into account (4). The overall incidence of AIH appears to be increasing in Denmark (1), and the prevalence of AIH is increasing in Sweden among both men and women (3).

PBC is a female-predominant disease (ratio ~9:1) that does not present in childhood and affects mainly patients aged older than 40 years. It is estimated that 1 in 1,000 women aged older than 40 years has PBC. In Europe, the estimated incidence rate is 1–2 per 100,000 population, and the prevalence ranges from 1.9 to 40.2 per 100,000. Global temporal trends show increased PBC prevalence (5). Although the annual age- and sex-adjusted incidence of PBC is not increasing in Alberta, Canada, the annual age- and sex-adjusted prevalence seems to be increasing (6).

The prevalence of PSC is 1–16 per 100,000 population, and it is more common among men (7). The overall incidence rate ratio of PSC for male compared with female patients is 1.70 (range 1.34–2.07), and the pooled median age at PSC diagnosis is 41 years (range 35–47 y) (8).
incidence rate estimates of PSC per 100,000 person-years at risk for population-based studies was 0.77 (range 0.69–1.14) (8). Various challenges exist in defining the epidemiology of PSC. It is frequently considered or suspected in patients with inflammatory bowel disease (IBD), but not formally diagnosed. In addition, 50% of patients are asymptomatic, and challenges exist in using diagnostic codes (International Classification of Diseases, 10th Revision) for PSC in databases. Five years after PSC diagnosis of asymptomatic patients, 20% will have developed clinical symptoms, and 75% will have evidence of disease progression, either from biochemistry liver tests or radiological findings.

**GENETIC PREDISPOSITION AND AILD**

Mendelian traits are strongly influenced by single-gene variation, whereas complex traits can result from variation within multiple genes and environmental interactions. AILDs are usually polygenic with no predictable inheritance patterns.

Evidence supporting the genetic contribution in AILD include familial predominance, twin studies, high sibling relative risks (RRs), candidate gene studies, and genome-wide association study (GWAS) results. Candidate gene studies are frequently associated with the human leukocyte antigen (HLA) in AILD and are limited by power and replicability (9).

The common disease–common variant hypothesis refers to the point that common variants in many genes lead to a small increase or decrease in disease risk. Although this may lead to advancements in the understanding of genetic architecture (beyond HLA), various limitations exist with the studies available, such as power and sample size, linkage disequilibrium, population differences, modest effect sizes, and unclear functionality.

Most non-HLA genetic variants are associated with more than one autoimmune disease, and a poorly defined collection of risk genes predisposes people to a variety of autoimmune conditions (10).

Pre-genetic studies of PBC indicate increased familial risk (~6%) in first- through fifth-degree relatives. Twin concordance is 0.63 with a sibling RR of 10.5. In addition, the high prevalence of anti-mitochondrial antibody (AMA) positivity has been demonstrated among first-degree relatives (FDRs), with a 4% risk of developing PBC among AMA-positive FDRs (10).

Most studies evaluating PBC candidate genes include HLA analysis. These studies suggest ethnic variability with HLA DRB1*0801 among European and North American Caucasians and HLA DRB1*0803 among Japanese. In studies from the United Kingdom, protective alleles include HLA DRB1*11 and HLA DRB*13. Some non-HLA candidate genes are tumour necrosis factor (TNF), cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1, interleukin (IL)-2, IL-10, IL-1, vitamin D receptor, and toll-like receptor (TLR). However, these studies are limited by low power and lack of replicability (11,12). Besides, HLA-DPB1 is associated with anti-sp100 positivity, HLA-DRB1*0405 is associated with anti-gp210, and HLA-DRB1*0803 is associated with anticentromere antibodies.

HLA risk alleles are uncommon (15%), with relatively small effect sizes. Dozens of non-HLA risk loci were identified, and the putative role of IL-12 is highlighted (13). IL-12 in PBC is heavily involved in Th1 response; variants at IL12A and IL12RB2 are the strongest and the most reproducible non-HLA associations in GWAS. Several upstream (interferon regulatory factor 5 [IRF5], suppressor of overexpression of constans 1 [SOCS1], nuclear factor kappa B subunit 1 [NFKB1], TNF Receptor Superfamily Member 1A [TNFRSF1A]) and downstream (tyrosine-protein kinase-2 [TYK2], signal transducer and activator of transcription 4 [STAT4] via Janus kinase/signal transducers and activators of transcription [JAK-STAT]) signals of IL-12 are associated with PBC (10).

PSC resembles the genetic architecture of other autoimmune diseases despite significant clinical differences (ie, male predominance, lack of response to immunosuppression). Autoimmune mechanisms may be upstream from biliary injury and fibrosis (14). More than 30 non-HLA genes have been described as associated with PSC and other autoimmune conditions (pleiotropy). These genes are a mixture of IBD susceptibility and loci from other autoimmune diseases (14). PSC–IBD genetic risk is complex, and only 5% of established risk loci in ulcerative colitis (UC) and Crohn’s disease (CD) have robust associations in PSC. Some PSC risk loci have no IBD associations (BCL2L11, FOXP1, SIK2, UBASH3A). Among IBD risk loci, causal variants of some PSC risk loci are independent of those of UC and CD (15). Also, PSC–IBD is genetically distinct from classic IBD (14,15).
Session 2: Mechanistic Themes in AILD

HOW DO ENVIRONMENTAL TRIGGERS DRIVE AILD?

Environmental factors such as bacteria, viruses, and xenobiotics have been studied as agents that may trigger AILD among susceptible individuals. Accordingly, the modulating role of genetic predisposition becomes key for understanding how environmental factors initiate disease. For example, patients with PBC have a higher prevalence of both infectious diseases and cancers, suggesting that they may have a lower resistance to infection (16). In fact, immunodeficiency and lymphopenia are known causes of autoimmunity. Therefore, the environmental cause of the disease pathology and the generation of an autoimmune response may be separate processes. Several theoretical mechanisms have been proposed to trigger autoimmunity. Molecular mimicry with shared host and microbial antigens can generate autoimmunity in animal models, and examples of superantigen activity have been reported in individual autoimmune diseases (17). Xenobiotic modification of host proteins and bystander activation with epitope spreading have both been demonstrated to trigger autoimmune responses (17). Pointedly, none of these processes have been proven to cause disease.

Various potential triggers, including *Novosphingobium aromaticivorans*, a human betaretrovirus (HBRV), xenobiotics such as octynoic acid, and modifying agents including cigarette smoking and female hormones, have all been linked with PBC (17). For example, specific *N. aromaticivorans* proteins and 2-octynoic acid–modified epitopes can bind AMAs, and both agents have been shown to provoke autoimmune biliary disease with production of AMAs in PBC animal models (17). However, *N. aromaticivorans* and xenobiotic 2-octynoic acid are not found in PBC patients' cholangiocytes, nor has either agent been directly linked with the disease process in clinical or interventional studies (Table 1). HBRV was cloned from PBC biliary epithelium, and multiple proviral integrations have been detected in PBC cholangiocytes (18). HBRV proteins have been found in cells expressing

| Test performed                            | Bacteria                     | Xenobiotic          | HBRV                           |
|-------------------------------------------|------------------------------|---------------------|--------------------------------|
| Serological reactivity                    | AMA binds *N. aromaticivorans* oxo-acid dehydrogenase proteins | AMA binds 2-octynoic acid modified haptens | AMA binds PDC-E2 and PBC-E3 binding proteins in virion particle |
| Detected in PBC cholangiocytes            | No                           | No                  | HBRV RNA and proviral integrations detected in PBC cholangiocytes |
| Triggers autoimmune phenotype of cell surface PDC-E2 expression in vitro | No                           | No                  | Co-cultivation of betaretrovirus with cholangiocytes |
| Detected with cell surface PDC-E2 expression in vivo | No                           | No                  | Viral proteins in PBC patients and mouse models |
| Mouse models                              | Triggers AMA production and cholangitis in NOD.1101 | Triggers AMA production and cholangitis | Significant reduction in hepatic biochemistry and cholangitis in NOD.c3c4 treated with combination antiretroviral therapy |
| Clinical trials                           | NA                           | NA                  | Significant reduction in hepatic biochemistry in PBC patients treated with antiretroviral therapy |

HBRV = Human betaretrovirus; AMA = Antimitochondrial antibodies; PDC = Programmed death cell; PBC = Primary biliary cirrhosis; NA = Not applicable
Autoimmune liver diseases

mitochondrial antigens on the cell surface, which is a disease-specific phenotype thought to break
tolerance to mitochondrial antigen (19,20). In cell
culture, HBRV infection triggers the same auto-
antigen expression in cholangiocytes (19), and
spontaneous PBC mouse models developing AMA
reactivity have been shown to express betaretrovi-
rus proteins in cells expressing mitochondrial anti-
gens as well (21). Antiretroviral therapy has been
used to treat the NOD.c3c4 mouse model with be-
taretroviral cholangitis, and various combinations
have been shown to inhibit betaretrovirus infec-
tion and ameliorate biochemical and histological
disease (22).

THE MICROBIOME AND AILD:
A NEW FRONTIER?

The abundant intestinal flora are tolerated through
complex host immune interactions. Disruption of
this balance has been implicated in the pathogen-
esis of several infectious and inflammatory gastro-
intestinal diseases. Antibiotics continue to occupy
an important part of therapeutic management of
these disorders, but this is complicated by loss of
bacterial diversity and incomplete microbial recov-
ery. Hence, restoration of healthy intestinal flora
through manipulation of the gut microbiome has
gained a lot of interest in the treatment of gastroin-
testinal diseases.

Fecal microbiota transplantation (FMT) is one
of the most commonly used ways to restore gut
microbial composition and functionality. It in-
volves the installation of minimally manipulated
microbial communities from the stool of a healthy
donor into a patient’s gastrointestinal tract (23).
According to US regulations, no investigational
new drug (IND) approval is required if it is used to
treat Clostridioides difficile infection (CDI) not re-
sponding to standard therapy. An IND is required
for any other indications such as clinical trials, and
informed consent should state that it is investiga-
tional and discuss real and theoretical risks. FMT
has an established role for recurrent CDI and is rec-
ommended by infectious disease and gastroenter-
ology clinical guidelines from North America and
Europe (24,25).

Clinical trials have demonstrated variable effi-
cacy of a daily antibiotic regimen on the improve-
ment in liver function tests (LFTs) among PSC
patients (32,33); however, there is concern regard-
ing the safety of long-term antibiotic use. Increased
risk for colonization by antibiotic-resistant strains
and subsequent bloodstream infections has been
reported (34).

Given the possible link between the microbi-
ome and PSC, an open-label FMT pilot study of
10 patients with PSC and co-occurring IBD was
conducted. All patients received a single FMT via
colonoscopy from the same donor. Blood and stool
were collected before FMT and through week 24.
There were no related adverse events, and 3 of 10
patients achieved the primary end point of a 50%
decrease in alkaline phosphatase (ALP) by week
24. Seven patients experienced a 30% decrease in at
least one of the biomarkers post-FMT. FMT shifts
taxa composition toward donors and causes global
community changes in microbiomes.

Engrafters strains were defined as strains that are
present in the donor, missing in patients pre-FMT,
and present in patients at 1 week post-FMT. En-
grafters in this study represented a diverse set of
taxonomic classes; however, an increase in overall
diversity at week 1 was not found to be associated

Microbial manipulation in liver disorders
Murine models provide preliminary evidence for
the involvement of gut microbiota in certain liver
conditions. As one example, preclinical data have
linked alterations in the microbiome to the patho-
genesis of AIH (28).

There has been growing interest in the possible
link between the gut microbiome and PSC, given
its link to IBD. Although the pathogenesis of PSC
remains unknown, it is hypothesized that bacterial
components may stimulate an aberrant immune
response, resulting in the perpetuation of the bili-
ary inflammation. It is also postulated that bacte-
ria gain access to the liver and biliary tree through
translocation across an abnormal and inflamed
intestinal mucosa into the portal venous system.
The majority of PSC cases co-occur with IBD, and
notably the gut microbiome of PSC patients has
overall lower biodiversity and is distinct from that
of healthy individuals as well as patients with IBD
alone (29–31).

Associations between the microbiome and vari-
ous chronic diseases have been observed, such as
IBD, irritable bowel syndrome, metabolic syn-
drome, obesity, and Parkinson’s disease (26,27).
Also, the intestinal microbiota have emerged as
a key environmental factor implicated in the de-
development of liver disorders through the gut–liver
axis.
with LFT improvement. Improvement in overall microbial diversity that persists and the abundance of engrafted operational taxonomic units present in patients post-FMT correlated with a decrease in ALP. Notably, this was the first human trial of FMT for the treatment of PSC, and it demonstrated that FMT is safe in this population (35).

BILIARY AUTOIMMUNITY AND PBC: THE JOURNEY FROM THE BILIARY EPITHELIUM TO THE PATIENT IN THE CLINIC (AND FROM PATIENT TO BILE DUCT AND BACK AGAIN)

The human face of PBC varies significantly, from asymptomatic disease to chronic cholestasis to features of end-stage liver disease, with jaundice, coagulopathy, hepatic encephalopathy, ascites, and gastroesophageal varices. Some features can be seen at all stages, including reduced quality of life, fatigue, cognitive impairment (dementia), and pruritus.

The pathological face of PBC is the classic bile duct lesion with portal tract granulomas. The immunological face of PBC is characterized by AMAs and anti-nuclear antibodies. AMA M2 can be positive in up to 99% of sera from PBC patients and are directed against the 2-oxo acid dehydrogenase complexes. In 2011, a GWAS study from the UK PBC consortium, including 1,840 cases and 5,163 controls (plus a replication sample), identified 12 new susceptibility loci for PBC (36).

Current challenges for a simple autoimmune model are based in biliary tropism when the antigen is ubiquitous and failure of intuitive immunotherapy (37).

Potential mechanisms for the environmental factor in PBC

The potential mechanisms are (1) exposure to an infectious agent with biliary tropism, (2) biliary concentration of a trigger factor, and (3) xenobiotic incorporation into the PBC autoantigen.

However, a clinical trial with ustekinumab, a monoclonal antibody against IL-12 and IL-23, among PBC patients under-responsive to ursodeoxycholic acid (UDCA) demonstrated no improvement in serum LFT (38). In addition, PBC has a characteristic proteome that is not modified by UDCA, and ALP levels are closely linked to inflammatory protein levels.

T-helper 17 (Th17) cells are elevated in the histological examination of inflammatory liver disease and peri-ductal areas in PBC (39).

A replicative senescence serves as a mechanism for the loss of progressive biliary epithelial cells and immunostimulation in PBC (40); biliary epithelial senescence and duct injury is present from disease outset among persons with high-risk PBC (41), and stressed cholangiocytes express senescence markers and lose function.

The senescence secretome induces IL-17 secretion by CD103+ T cells in PBC, and this could be a mechanism for interface hepatitis, sometimes present in PBC, and IL-12 expression by senescent bile duct cells might identify the very-high-risk phenotype in PBC.

Pre-treatment liver transcriptome might predict the outcome and treatment need in PBC (41).

Generations of treatment in PBC

The first-generation treatment is UDCA; second generation, obeticholic acid (OCA; index farnesoid X receptor [FXR] agonist); third generation, new generation anti-cholestatics (eg, MBX 8025); and fourth generation, targeted combination therapy in high-risk patients to achieve disease modification or remission, and maybe senolytics.

Goals of therapy

1. Reduce the risk to life or need for transplant associated with liver failure or progression to cirrhosis, focused on prevention of the development of fibrosis or cirrhosis and ductopenia.
2. Improve patients’ quality of life and functional status, focused on clinical features of cirrhosis, pruritus, and fatigue or cognitive impairment.

IS B-CELL DEPLETION THERAPY THE MISSING BULLET FOR NEW AILD THERAPIES?

In AIH, T cells are pathogenic, and B cells present antigens to T cells. Autoantibodies are frequently present, but their role in the pathogenesis is unclear. CD20+ B-cell depletion alters T-cell homing, and the success of B-cell depletion is caused by reduced activation of T cells and their retention within lymphoid organs (42). The following mechanisms by which B-cell depletion causes liver inflammation remission have been proposed. B-cell depletion restores T follicular helper cells in secondary lymphoid organs. It reduces auto-antigen
Autoimmune liver diseases presentation by B cells but also by antigen-presenting cells (APCs) in the spleen and the liver. This decreases T-cell activation and a positive feedback loop between B and T cells. Besides, B-cell depletion abrogates a source of pro-inflammatory cytokines in the liver.

Rituximab, an anti-CD20 monoclonal antibody, was safe and well tolerated and resulted in biochemical improvement among patients with refractory AIH (43). Other treatments that could be evaluated in the future include ocrelizumab, another anti-CD20 monoclonal antibody (Ocrevus; Genentech/Roche, San Francisco, CA) that is administered as two intravenous infusions of 300 mg given 2 weeks apart and is conditionally approved by Health Canada and the US Food and Drug Administration for early primary progressive multiple sclerosis. Ublituximab (TG-1101) is a monoclonal antibody that targets a unique epitope on the B lymphocyte CD20 antigen. Anti-CD79 antibody induces B-cell anergy that protects against autoimmunity. CD79 is a transmembrane protein (heterodimer) that forms a complex with the B-cell receptor (BCR) and generates the signal after recognition of the antigen by the BCR (44). Also, the use of B-cell activating factor receptor (BAFF-R) antibodies in repeated doses was efficient in the control of liver inflammation in an animal model of AIH, and a clinical control trial is ongoing.

Session 3: Treatment Paradigms

PBC: FROM ESTABLISHED TO NEXT-GENERATION THERAPIES

The use of UDCA has multiple therapeutic effects for PBC patients, including biochemical improvement, metabolic effects, delayed histologic progression, delayed appearance of esophageal varices, and improvement in liver transplantation (LT)-free survival. However, approximately 40% of PBC patients are considered non-responders to UDCA (Table 2). Risk factors for suboptimal response include diagnosis at a young age, male gender, Hispanic ethnicity, and advanced disease stage.

OCA is an FXR agonist. It is a second-line agent with anti-inflammatory and anti-fibrotic effects with metabolic benefits. Using modelling tools, combination therapy with UDCA was shown to reduce the predicted 15-year cumulative incidence of decompensated cirrhosis, hepatocellular carcinoma (HCC), liver-related mortality, and need for LT (45).

Although improvement in LT-free survival has not yet been demonstrated in prospective studies, OCA is conditionally approved in North America and Europe for use in combination therapy with UDCA in PBC patients with an incomplete response after at least 1 year of UDCA therapy or as monotherapy for those who are intolerant to UDCA. Pruritus is the main side effect, affecting up to 48% of patients, and in the real world, 15%–25% of patients discontinue the medication for this reason.

Fibrates have also been evaluated for PBC management and are currently used as off-label options.

Table 2: Evaluation of biochemical response to UDCA among patients with PBC

| Scores | Time (mo) after UDCA initiation | Definition of non-responders or scoring parameters |
|--------|--------------------------------|--------------------------------------------------|
| Binary definitions | | |
| Rochester | 6 | ALP ≥2 ULN or Mayo score ≥4.5 |
| Barcelona | 12 | Decrease in ALP ≤40% and ALP ≥1× ULN |
| Paris I | 12 | ALP ≥3× ULN or AST ≥2× ULN or bilirubin >1 mg/dL |
| Rotterdam | 12 | Bilirubin ≥1× ULN and/or albumin <1× ULN |
| Toronto | 24 | ALP >1.67× ULN |
| Paris II | 12 | ALP ≥1.5× ULN or AST ≥1.5× ULN or bilirubin >1 mg/dL |
| Ehime | 6 | Decrease in GGT ≤70% and GGT ≥1 ULN |
| Continuous scoring | | |
| UK-PBC | 12 | 12 mo: bilirubin, ALP and AST (or ALT) Baseline: albumin and platelets |
| GLOBE | 12 | 12 mo: bilirubin, ALP, albumin, and platelet count Baseline: age |

UDCA = Ursodeoxycholic; ALP = Alkaline phosphatase; ULN = Upper limit of normal; AST = Aspartate aminotransferase; GGT = Gamma-glutamyl transferase
Fibrates are peroxisome proliferator-activated receptors (PPAR) agonists with anti-inflammatory and regulatory effects in bile acid synthesis and metabolism. The BEZURSO trial compared UDCA plus bezafibrate combination with UDCA plus placebo in incomplete responders. Use of combination therapy led to ALP normalization in 67% of UDCA non-responders and normalization of all liver biochemistries in 30% of UDCA non-responders at 2 years (46). In a post hoc analysis, the UDCA plus bezafibrate combination therapy was associated with prolonged predicted survival; however, the incomplete response rate was 30% on the basis of Paris II criteria, and risk factors for incomplete response on multivariate analysis were presence of portal hypertension and high levels of ALP at baseline (>2.5× upper limit of normal [ULN]). Notably, even these patients with incomplete response had a reduction in the predicted mortality or need for LT (47).

Regarding symptom control, the FITCH trial demonstrated that bezafibrate was superior to placebo in improving pruritus in chronic cholestatic liver disease (48), and OCA plus bezafibrate combination therapy had a strongly positive effect on cholestasis, improved pruritus, and was well tolerated (49).

Other novel therapies, such as cilofexor (FXR agonist) and seladelpar (PPAR-δ agonist) in phase II studies, demonstrate promising biochemical response rates in PBC patients. Elafibranor (dual PPAR-α+δ agonist) has demonstrated favourable efficacy and safety among PBC patients with an inadequate UDCA response in a phase IIa trial (50). Other agents such as GKT831 (NADPH oxidases [NOX] 1+4 inhibitors) are also being studied in ongoing trials, with encouraging interim results showing improvement in gamma-glutamyl transferase (GGT), ALP, and liver stiffness measurements (51,52).

The use of antiretroviral therapy repurposed to treat HBRV infection has been reported in two randomized controlled trials (RCTs) using PBC patients unresponsive to UDCA. In a phase II lamivudine–zidovudine study, patients did not achieve the stated end points, but those on therapy developed a significant reduction in ALP (53). A case history reporting normalization of liver tests in a person with PBC using tenofovir–emtricitabine and ritonavir (54) was followed by a second RCT using the same combination. Enrolment was curtailed early because two-thirds of patients developed side effects from lopinavir–ritonavir (55). Nevertheless, the open-label extension study showed that patients who remained on combination therapy developed sustained improvement in hepatic biochemistry and HBRV levels. A second multi-centre Health Canada–approved study using tenofovir–emtricitabine and raltegravir is underway.

**AIH: WHERE IS THE FUTURE OF TREATMENT HEADING?**

AIH is associated with decreased life expectancy and poor quality of life. Treatment goals include achieving remission and preventing disease progression, liver-related mortality, and the need for LT. AIH standard-of-care (SOC) treatment includes either steroid monotherapy or a combination of steroid and azathioprine. Alternative immunosuppressive agents for non-responders include mycophenolate mofetil (MMF), tacrolimus, and cyclosporine, among others. Achieving biochemical remission has the potential to prevent the progression of fibrosis to cirrhosis and reduce the risk of hepatic-related death or need for LT. Real-world data indicate a substantial rate (40%–50%) of failure to achieve complete remission with SOC treatment. Hence, new therapies are needed to achieve remission in those failing SOC treatment, followed by the prevention of long-term complications. Ianalumab, a monoclonal antibody against BAFF, is a novel AIH therapy currently being evaluated in a phase II clinical trial. Ianalumab causes rapid, long-lasting depletion of B cells (but not plasma cells) that is mediated by antibody-dependent cellular cytotoxicity and sustained by modulating B-cell receptors for BAFF (hence, the name of the trial is AMBER, an acronym for ADCC-Mediated B-Cell depletion and BAFF-R Blockade). Other novel treatments are emerging, such as pre-implantation factor (which prevents maternal rejection of an allogeneic embryo), TLR-4 inhibitors, JAK inhibitors, and Th17 cell inhibitors.

**TREATMENT OF AILD IN CHILDREN: WHAT ARE THE DISTINCTIONS AND UNMET NEEDS?**

Management of pediatric AILD is broadly similar to that of adult AILD. Careful phenotyping of pediatric patients to optimize the choice of drugs and improve outcomes is advocated. Among
adolescents, for whom a cosmetic-related adverse event profile is particularly important, using steroid-sparing agents in combination with budesonide is helpful. This strategy encourages good adherence to therapy and ultimately better outcomes with more sustained remission of disease, particularly among teenagers. A steroid-sparing approach is also important for those with elevated BMI and co-existent hepatic steatosis with or without other components of the metabolic syndrome. Adolescents are prone to acne, and drug-induced AIH after ingesting minocycline is not uncommon; stopping the medication is necessary before embarking on other therapy. Among some ethnic minorities, there is presentation of severe disease early in life, resistance to standard therapy, or both. Awareness of these and moving on to second- or third-line therapy early in the course of disease allows for a higher chance of disease remission and can reduce progression to end-stage liver disease. AIH overlaps sclerosing cholangitis (referred to as autoimmune cholangitis, in which biliary changes are seen), elevated GGT, biliary dilation or narrowing on imaging, and bile ductular proliferation or paucity in addition to the classical features of AIH. Addition of UDCA to the immunosuppressive regime is customary, but it does not appear to halt the progression of disease. Wilson disease can mimic AILD and should be ruled out, particularly if there is non-response to immunosuppression. Monitoring adherence is crucial in managing pediatric patients with AILD, particularly before escalating treatment. With younger children, parents take responsibility for administering medication, but teenagers usually take medications on their own. Objective measures, including measurement of azathioprine metabolites (6-thioguanine and 6-methylmercaptopurine), are helpful in assessing adherence and dose optimization. Management of recurrent AIH is similar to that in adults. De novo AIH—the occurrence of AIH in pediatric LT recipients who are not transplanted for AIH—appears to be a different entity in children than in adults.

Current unmet needs in pediatric AILD management include a better understanding of the pathogenesis and the need for more RCTs, particularly in the setting of new options after standard therapy has failed. Experience with rituximab and infliximab is limited, although new promising agents such as ianalumab are being studied in the adult population.

SYMPTOMS AND AILD: FROM BURDEN TO INTERVENTION

AILD leads to multiple burden of symptoms, most notably fatigue, pruritus, and psychological stress. In patients with PBC, young age and disease duration are risk factors associated with fatigue. Fatigue has been demonstrated to reduce quality of life and cognition, and it increases mortality. Eighty percent of patients with early-stage PBC report cognitive impairment (19% severe and 34% moderate) (56), and fatigue is associated with reduced LT-free survival (77% versus 60% at 9 y) (57). These effects are probably mediated by a combination of autonomic, central nervous system, and muscle dysfunction, together with disordered sleep patterns. These symptoms are independent of the UDCA response. Fatigue does not qualify for Model for End-stage Liver Disease (MELD) points in LT, and it needs to be managed comprehensively to provide optimal care. Pruritus is another symptom frequently undertreated by clinicians. Bezafibrate (FITCH trial) has been demonstrated to achieve a more than 50% reduction in visual analogue scale score among 38% of patients with chronic cholestasis compared with 12% in the placebo group (48). Ileal bile acid transport inhibitors are also promising for pruritus management.

It is important to be aware of extrahepatic manifestations, most commonly Sjögren’s syndrome, thyroid dysfunction, and scleroderma. Although objective symptoms should not be minimized, psychological stress and uncertainty of prognosis are associated with depression and reduced quality of life, particularly among PSC patients.

Session 4: Clinical Trials—Approaches and Challenges to New Therapies

PBC: LESSONS LEARNED FROM THE JOURNEY OF SURROGATES AND DRUG DISCOVERY

PBC biochemical response criteria include various scores (Table 2). New dimensional scores include the UK-PBC risk score (58), and more recently an international scoring system (the GLOBE score) was developed and validated to predict LT-free survival of UDCA-treated patients with PBC (59).
The Global PBC study group is an international network of 23 liver centres in 15 countries that has allowed the meta-analysis (retrospective) of individual patient data from major long-term follow-up cohorts from individual centres with more than 6,000 PBC patients, more than 49,000 patient visits, and more than 20 years follow-up.

**Lessons learned**
The top three challenges are (1) convincing clinicians of the added value of retrospective historical databases, (2) improving quality and proof of feasibility, and (3) working with different institutional review boards and legal departments.

The top three successes have been (1) revival of the AILD community, encouraged by new treatments; (2) the new second-line treatment options and new emerging treatments, and (3) the better and deeper understanding of the disease and patients’ unmet needs.

What has worked well are the joined forces, identification of non-responders and why working alone in a rare disease does not benefit anyone, and the spin-off to other rare liver diseases for children.

The Canadian Network for Autoimmune Liver disease (CaNAL) was initiated in 2016 to assess geo-epidemiological differences and FibroScan changes over time and to capture the new treatment era in Canada for PBC and AIH (and their overlap). So far, more than 3,000 patients have been included in the retrospective arm of the CaNAL database, and the prospective arm currently includes 679 patients providing lifestyle and quality-of-life data. Edmonton, Montreal, Kingston, Saskatoon, and Toronto are active sites. Calgary, Ottawa, Vancouver, and Halifax are also participating, and Hamilton, Vancouver, and Thunder Bay are upcoming sites. The first output of CaNAL, a large real-world experience with 65 patients and more than a year of follow-up, was to investigate the use of OCA with UDCA in patients with high-risk PBC. Seventy percent of patients met POISE (Perioperative Ischemic Evaluation) inclusion criteria, and 30% met other risk criteria (60).

**PSC: A STORY OF THERAPEUTIC OBSTACLES BUT RENEWED OPTIMISM?**

Various prognostic models have been developed to predict survival in patients with PSC. The Mayo Clinic model considers age, hepatomegaly, histologic stage, hemoglobin, and IBD; the King’s College model considers age, hepatomegaly, histologic stage, splenomegaly, and ALP.

Other prognostic models include the Amsterdam–Oxford model that considers PSC subtype, age at diagnosis, albumin, platelets, AST, aspartate aminotransferase (ALP), and bilirubin (61). The PSC risk estimate tool (PREsTo) consists of nine variables: bilirubin, albumin, ALP × ULN, platelets, AST, hemoglobin, sodium, patient age, and number of years since PSC was diagnosed (62). The UK-PSC risk scores for short-term and long-term outcome prediction are based on age, bilirubin values, ALP, albumin, platelets, presence of extrahepatic biliary disease, and variceal hemorrhage (63).

The AESOP trial is a randomized, double-blind, placebo-controlled, phase II study of OCA in patients with PSC (64). In a randomized, placebo-controlled, 12-week phase II study, the non-steroidal FXR agonist GS-9674 was associated with significant improvements in liver biochemistry tests and markers of cholestasis without aggravating pruritus in patients with PSC (65). However, not all recent trials have been positive. Efficacy and safety of simtuzumab for the treatment of PSC was investigated in a phase 2b, dose-ranging, randomized, placebo-controlled trial (66). Although simtuzumab was safe, no benefit was noticed among patients with PSC.

**TRIALS AND CHILDHOOD AILD: HOW TO DELIVER NEW THERAPIES?**

Clinical trials should be conducted with children with AILD because they have different physiology and different clinical needs. Off-label drug use and lack of efficacy and toxicity data are additional reasons to conduct clinical trials with children; however, ethical, physiologic, pharmacokinetic, age-specific, logistic, and disease-specific challenges exist.

There is a dilemma in finding a balance between the obligation to conduct trials to protect children from the risk of using medicines untested in pediatric populations and to protect children from the unknown risks and harms that may occur with clinical trial participation. Young children may not understand the risks involved in trials and therefore depend on adults to make decisions for them.

For young children, the parent or guardian gives informed consent, although they themselves
may not feel burdened by the study requirements. Older children and adolescents, who are capable of understanding the risks and benefits of a trial, provide their own informed consent. In most regions, there is no specific age of consent; rather, it is judged on a case-by-case basis. Typically, though, 12–14 years is the age at which children may begin to have sufficient developmental maturity to provide informed consent.

Assent should be obtained from children who do not have the capacity to provide formal informed consent. Of all the children aged 6–8 years who were invited to participate in a vaccine study, two-thirds understood they would have a blood test, but two-thirds did not know why. In addition, three-quarters of parents felt they alone should make the decision, whereas half of children felt they were old enough (67).

Most pediatric trials have small sample sizes; only 38% of published pediatric trials had samples larger than 100 (68). Lower burden of disease among children makes recruitment more difficult. The rarity of certain important outcomes is an added challenge to achieving adequately powered trials. Azathioprine, cyclosporine, and tacrolimus may be metabolized more quickly by young children and require a higher dose per kilogram than adults. Increased total body water concentration in children requires a lower concentration of hydrophilic drugs.

There are also unique phenotypic considerations in AILD in children. Autoimmune sclerosing cholangitis, as mentioned, is more common among children than among adults. The prevalence among adults is 1.4%–8% (69,70), whereas in an international series of 781 pediatric patients, the prevalence of AIH in children with PSC was 33% (71). Uncertainty in rates of progression to liver disease with clinically meaningful outcomes is currently a major barrier to drug development (72,73).

Age has an impact on disease severity and natural history. Therefore, a question that arises is whether the same treatment outcomes can be expected among children as among adults when the natural history is different.

The limited acceptance of biopsy for pediatric research by parents and research ethics boards, lack of validation of surrogate fibrosis biomarkers, and few validated disease activity scores are all additional challenges in pediatric liver disease research (73).

Session 5: Looking Beyond Traditional Disease Boundaries

GENDER AND AILD: PREGNANCY AND BONE HEALTH

In a normal pregnancy, Th2 immune response is predominant with humoral, antibody-associated IL-4, IL-5, IL-6, IL-9, and IL-10 cytokines, whereas in PBC, PSC, and AIH, Th1 immune response is predominant with cell-mediated phagocytosis and interferon-\(\gamma\), TNF-\(\beta\), and IL-2 cytokines.

Patients with AILD have a higher risk of spontaneous abortion, premature delivery, pre-eclampsia, and intrauterine growth restriction (IUGR). Few studies on AILD and fertility exist. PSC and AIH have no impact on fertility. PBC, IBD, systemic lupus erythematosus, thyroiditis, and type 1 diabetes mellitus are associated with pregnancy loss, endometriosis, and premature ovarian failure (74–77).

Pregnancy is rare among patients with cirrhosis (77,78). In a study of 62 women, with 27 AILD cases, the live birth rate was 58%, with fetal loss and elective termination similar to that among the general population. MELD correlated with risk in pregnancy; a MELD score higher than 10 increased the risk of maternal complications, whereas a MELD score less than 6 was associated with a good pregnancy outcome. Esophageal varices can occur in up to 50% of pregnant patients screened. Starting beta-blockers (IUGR, bradycardia, hypoglycemia) and octreotide (possible risk of uterine ischemia) should be avoided; however, beta-blockers can be continued because stopping may elicit rebound variceal bleeding (77).

PSC was associated with an increased risk of elective caesarean section, with a 2.18-fold increase (95% CI 1.50–317). This increased risk did not show any significant association with IBD.

Regarding disease-related outcomes in PSC, liver biochemistry tests (bilirubin, ALP ± ALT > 2 × ULN pre-partum) increased during (20%) and after (32%) pregnancy. Regarding other complications, 30% had existing pruritus, which was stable in 60%, and de novo pruritus occurred in 12% (79,80). PSC was also associated with an increased risk of preterm delivery (79,80).

Disease flares are common in AIH, with 11%–30% occurring during pregnancy. The majority of reported flares during pregnancy occur despite pharmacologic treatment and respond to
corticosteroids. In 20% of patients, a flare led to hepatic decompensation, and up to 52% of flares were reported postpartum (81–83).

Although some medications, including prednisone, azathioprine–6-MP, cyclosporine, tacrolimus, and infliximab are considered safe during pregnancy, MMF and rituximab are contraindicated. Prednisone and prednisolone (Class C) increase the risk of cleft palate in the first trimester. Budesonide appears safe, though there is a paucity of studies. Minimal levels of prednisone were detected in breast milk, with no data for budesonide, and recommendations are to counsel and continue. Azathioprine and 6-MP (Class D) showed no association with adverse outcome in AIH. In large studies with patients with IBD, no maternal or fetal risk was noticed (Class D, due to teratogenicity in animals). MMF is teratogenic and not recommended for use in pregnancy.

Rituximab is associated with preterm birth, hematologic abnormalities, increased risk of infection, and possible congenital malformations. The recommendation is to avoid pregnancy for at least 12 months after use (84–86).

Pre-existing pruritus worsened in 57% of patients with PBC, and de novo pruritus was reported in 53%, of whom 71% required specific therapy. Biochemistry findings are stable throughout pregnancy in the majority of patients (70%) but might get worse postpartum (72%).

Worse pregnancy-related outcomes were not reported (76,87). Safe medications include UDCA, antihistamines, sertraline, and rifampin; naltrexone, fibrates, OCA, and gabapentin are unsafe or their safety is unknown (88).

For fibrates and OCA, safety data and excretion into breast milk are unknown; therefore, avoiding their use is recommended. Although antihistamines are safe, cholestyramine is likely to be safe; however, it reduces the absorption of ADEK vitamins and might be associated with fetal hemorrhage (one report).

HOW TO TRANSITION THE PEDIATRIC PATIENT WITH AILD TO ADULT CARE

In North America, 750,000 adolescent and young adult patients with chronic pediatric conditions transition into adult-based care every year, and 75% of pediatric patients with acquired or congenital liver disease survive into adulthood (89). Transition is defined as a purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems (90).

Heldman et al conducted a national survey of adult transplant hepatologists (91). The response rate by all United Network for Organ Sharing centres was almost 60%, and participants were asked to identify key barriers to a successful transition of care (19-item survey). They concluded that fewer than half (46%) of transitioning patients had adequate knowledge of the condition, their medications, and indications for use. More than one-third arrived at the first clinic without a parent or guardian or another adult. Only 15% of programs had a formal transition program, and hepatologists reported that barriers to successful transition were poor adherence to medications, laboratory testing, and follow-up clinic visits and inadequate knowledge of past medical history.

Non-adherence was reported by 35%–50% of adolescent patients (92), and it was four times more common among children and teenagers than among adult LT recipients (93). Factors associated with worse adherence to treatment were female sex, lower socio-economic status, being a single parent, and being a teenager at the time of LT. According to the World Health Organization report on non-adherence (94), socio-economic, patient-related, condition-related, treatment-related, and health care delivery–related factors make up important categories of risk.

Non-adherence is difficult to detect because whether it is a partial or complete absence of adherence may not be clear and also because objective and accurate measurement methods are lacking (94). In the LT population, the strongest indicator is variability in immunosuppression levels (95). Psychological factors associated with poor adherence (93) are low self-esteem, social adjustment issues, behavioural issues, family function status, and post-traumatic stress disorder (96).

Transfer of pediatric care to adult care (97) consists of various stages of transition, specifically early transition around ages 10–12 years, middle transition at ages 13–15 years, and late transition at around age 16 years and older (Figure 1).

To determine readiness, adolescents should be able to describe their health condition, demonstrate responsibility for health management tasks, and show capacity to independently manage health care needs (98). However, it should be noted that there is no perfect program. A 2011 position
Autoimmune liver diseases statement by the American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians outlined six core elements of health care transition: transition policy, transition tracking and monitoring, transition planning, transfer of care, and transfer completion (99).

IS THERE A REAL BURDEN FROM RECURRENT AILD POST–LIVER TRANSPLANT?
AILDs constitute the third most common indication for LT (100). Overall, patient and graft survival after LT of these patients is acceptable, with 5-year survival rates of around 77%, 73%, and 74% for PBC, PSC, and AIH, respectively (101). Recurrence rates vary across different studies depending on the length of follow-up, whether biopsies were done by protocol or per clinical indication, and the criteria used to define recurrence.

**Recurrent AIH**
Recurrent AIH (rAIH) increases with time after LT with 1- and 5-year rates of 8%–12% and 36%–68%, respectively (102,103). A systematic review calculated a 23% recurrence rate after a median of 26.4 months (range 14.4–55.2 mo). Notably, patients may have rAIH with normal liver tests. Histopathological changes can precede biochemical recurrence by as much as 9 years. A timely diagnosis of rAIH is important to start treatment and modify the course of the disease (Table 3). There are no controlled trials for rAIH, but in most cases when there is only mild activity on liver biopsy or recommencement of or an increase in the dose of corticosteroids, optimization of azathioprine with monitoring of metabolite levels is enough (104).

Clinical outcomes of how rAIH affects LT are discordant, but the balance seems to tilt toward their having a negative impact on patient and graft survival. Some studies show that 5%–18% of patients will develop fibrosis progression, and 6.2%–50.0% may experience graft loss due to rAIH and require retransplantation (102). A recent multi-centre study including 480 patients (74% female) with AIH among 17 centres in North America, Europe, South America, and Asia described rAIH in 24% after 5 years and in 41% after 10 years. The main risk factors for rAIH were being aged younger than 40 years at LT (hazard ratio [HR] = 1.74; p = 0.04) and ALT higher than 1.5 ULN 12 months post-LT (HR = 3.55; p <0.001). More important, the use of low-dose prednisone after LT reduced the risk of rAIH (HR = 0.48; p = 0.01). rAIH was associated with a higher risk of graft loss (HR = 4.53; p <0.001) and patient overall survival (HR = 1.95; p = 0.02) (105).

**Recurrent PBC**
The median time to rPBC is usually 3.5–5 years. Rates of rPBC vary across studies, depending on the criteria used to define rPBC and on whether protocol or clinically driven biopsies were made. For example, in a previous study with clinically driven biopsies, the 5- and 10-year recurrence rates...
Table 3: Diagnostic criteria for recurrence of autoimmune liver disease after liver transplantation

| Recurrent Disease | Diagnostic criteria |
|-------------------|---------------------|
| rAIH              | History of liver transplantation related to AIH  
Hypergammaglobulinemia; increased serum IgG levels; and ANA, SMA, or both ANA and SMA  
Histological aspects* (prominent lymphocytic interface activity with or without plasma cell infiltration, acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells, pseudo-rossetting of hepatocytes, and perivenular lymphoplasmacytic inflammation, confluent and bridging necrosis with lymphoplasmacytic infiltration [severe inflammatory activity]) |
| rPBC              | History of liver transplantation related to PBC  
Confirmed diagnosis of PBC in the explant histology with characteristic histologic features (lymphoplasmacytic portal infiltrate, lymphoid aggregates, epithelioid granulomas, evidence of bile duct injury)  
Persistence of AMA or AMA-M2  
Exclusion of other causes of graft dysfunction (acute and chronic rejection, graft versus host disease, bile flow impairment or cholangitis, vascular complications, viral hepatitis, drug-induced hepatitis) |
| rPSC              | Confirmed diagnosis of PSC before LT  
Cholangiography showing non-anastomotic intrahepatic and/or extrahepatic biliary strictures with beading and irregularities of bile ducts at least 90 d after LT and/or histopathological findings of fibrous cholangitis and/or fibro-obliterative lesions  
Exclusion of other causes of graft dysfunction (hepatic artery thrombosis or stenosis, chronic ductopenic rejection, anastomotic and non-anastomotic strictures before day 90 after LT, ABO-incompatible LT) |

*Features may be less pronounced, absent, or otherwise atypical in part because of concurrent antirejection therapy  
r = recurrent; AIH = Autoimmune hepatitis; IgG = Immunoglobulin G; ANA = Antinuclear antibodies; SMA = Smooth muscle antibodies; PBC = Primary biliary cholangitis; AMA = Antimitochondrial antibodies; PSC = Primary sclerosing cholangitis; LT = Liver transplantation

were 13% and 29% (106), respectively, whereas in a study with protocol-guided biopsies, the recurrence rate was higher, as expected, with 5-, 10-, and 15-year rates of 27%, 47%, and 61%, respectively (107).

Younger age at diagnosis and at the time of LT is associated with a higher risk of rPBC (108). Among men, biochemical markers of cholestasis within the first year after LT are also associated with rPBC (108). Tacrolimus, when compared with cyclosporine, has been associated with rPBC, and also with an earlier and more aggressive course (106).

The standard treatment for rPBC is UDCA. However, unlike in pre-LT patients, the use of UDCA has not been shown to modify the natural history of rPBC in the short or medium term, even after improving ALP levels. Data are also lacking regarding the use of second-line treatments, such as OCA or bezafibrate, for non-responders to UDCA in the post-LT setting. The preventive administration of UDCA started within the first 2 weeks after LT was associated with a lower risk of rPBC (107) (Figure 2). A recent multicentric study found rPBC to be associated with worse graft and patient survival after LT. In addition, overall survival was lower among patients with rPBC than among those with no recurrent disease (108).

Recurrent PSC

The recurrence rate of PSC is variable across the different studies depending on the criteria used to define recurrence and the median follow-up. The 1-, 5-, and 10-year recurrence rates range among 2%–5%, 12%–60%, and 20%–50% (109), respectively, with a median time to recurrence of 4.6 years (range 6 mo–5 y).

Intact colon before LT and the presence of UC post-LT (109,110) were found to increase the risk of rPSC. These factors underscore the interplay between the bowel and the liver in PSC patients. Other risk factors associated with rPSC are young age at LT (110), HLA-DRB1*08 in the recipient, male recipient, cytomegalovirus infection, cholangiocarcinoma (CCA) in the native liver, overlap syndrome, high MELD at the time of LT, and the need for maintenance steroids (>3 mo) for UC post-LT (110).

rPSC diagnosis is based on cholangiography showing non-anastomotic intra- or extrahepatic biliary strictures with beading and irregularities of
bile ducts at least 90 days after LT, histopathological findings of fibrous cholangitis, fibro-obliterative lesions, or all of these.

Currently, there is no effective way to prevent rPSC. Even though there is a clear association between IBD and recurrence, the role of prophylactic colectomy needs to be further assessed. A recent Nordic multicentre study found tacrolimus to be associated with rPSC; if confirmed, using an alternative drug could provide an effective means to prevent recurrence (111).

Patients who develop rPSC have decreased graft, re-LT free, and patient survival compared with patients with no recurrence (109,110). There seems to be an interaction between age and rPSC because patients aged younger than 40 years at the time of LT are at increased risk of graft failure. Graft loss due to rPSC is variable depending on the follow-up, and from 25% to 50% of those who are re-transplanted are reported to be due to rPSC. In long-term follow-up studies, 30%–50% of patients who had graft failure developed it because of rPSC.

**CCA AND PSC: CAN WE SEE HOPE AHEAD THROUGH SCIENCE AND SURGERY?**

CCAs are classified on the basis of their anatomical location into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) subtypes. pCCA is the CCA subtype that arises in the setting of PSC. PSC is an important CCA risk factor; late-onset PSC and prolonged duration of IBD are associated with a higher risk of CCA, whereas the risk of CCA is lower among those with small-duct PSC and among pediatric patients. CCA remains one of the leading causes of mortality in PSC patients, accounting for one-third of all deaths in a population-based series, and it has an annual incidence rate of 1%–2% (65,112–115).

MRI with magnetic resonance cholangiopancreatography (MRCP) has superior sensitivity and specificity at 88% and 85%, respectively, compared with other imaging modalities such as CT scan or positron emission tomography scan. Hence, MRI with
MRCP is the imaging modality of choice for CCA surveillance in PSC patients (Table 4). A malignant-appearing mass with delayed venous enhancement is nearly 100% specific for CCA (116–118).

Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used biomarker for detection of CCA. CA 19-9 of more than 129 U/mL has a sensitivity of 79% and specificity of 99% for CCA detection (119,120). Some patients with PSC might have elevated CA 19-9 without CCA, including those with persistent cholestasis, recurrent bacterial cholangitis, and extrahepatic malignancy. Routine biliary cytology has a subpar sensitivity (10%–40%) for CCA detection. However, it remains the gold standard because of its high specificity (97%–100%) (121,122). Cytological assessment is limited by sampling errors, desmoplastic and paucicellular specimens from tumours that can reside in difficult-to-access areas, and subjective diagnostic criteria.

Fluorescence in situ hybridization (FISH) analysis, which is defined as four or more epithelial cells with two or more signals in two or more loci, has enhanced sensitivity compared with conventional biliary cytology (123). FISH polysomy is a marker of chromosomal instability (Figure 3).

### Treatment of CCA

Neoadjuvant chemoradiation plus LT is a treatment option for pCCA. Inclusion criteria for this protocol include radial diameter of tumour of less than 3 centimetres and absence of intra- or extrahepatic metastatic disease. The neoadjuvant chemoradiation includes external beam radiation therapy with concomitant 5-fluorouracil followed by brachytherapy. Patients are subsequently maintained on oral capecitabine until the time of transplant. Before transplant, patients undergo hand-assisted laparoscopic staging.

Systemic therapy is the SOC for patients with advanced CCA who are not eligible for surgical intervention.
Autoimmune liver diseases resection or LT. Emerging systemic therapies for CCA are targeted therapy and immunotherapy. Gemcitabine–cisplatin plus nab-paclitaxel has been tested in an open-label, single-arm, phase 2 trial with 60 patients enrolled. Of those 60, 38 (63%) had iCCA, 9 (15%) had pCCA–dCCA, and 13 (22%) had gallbladder CA; 78% of the patients had metastatic disease. Median progression-free survival (PFS) (primary end point) was 11.8 months, and the median overall survival was 19.2 months. A phase 3 RCT is currently underway (124).

Targeted therapies include inhibitors of fibroblast growth factor receptor (FGFR). BGJ398, a pan-FGFR kinase inhibitor, was investigated in a phase II clinical trial with 61 patients, including 48 with FGFR2 fusions. The overall response rate was 14.8%, with a median PFS of 5.8 months and disease control rate of 83.3%. The median duration of disease control was 7.5 months (125,126).

Immunotherapy is an emerging option for advanced-stage CCA. A multi-cohort phase 2 study of the programmed death 1 inhibitor pembrolizumab included 104 patients with previously treated advanced CCA. The objective response rate (ORR) was 5.8% with a 5.8% partial response. There was no correlation of ORR with programmed death-L1 expression (127).

It is still unclear which patients have a higher propensity to develop CCA, and therefore better risk stratification is needed. Germline mutations that predispose PSC patients to CCA (GWAS) need to be investigated in future studies. Chemopreventive strategies with aspirin, detection of early-stage disease by developing tumour biomarkers in biological specimens, and curative nonsurgical treatment of malignancy arising in the setting of PSC should be the emphasis of future studies.

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