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Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease

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Summary

Background: Improved knowledge of the molecular pathophysiology and immunopathogenesis of cholestatic liver diseases in recent years has led to an increased interest in developing novel therapies. Patients with cholestatic liver disease often require different approaches to assessment and management of suspected drug-induced liver injury (DILI) compared to those with healthy livers and those with parenchymal liver diseases. At present, there are no regulatory guidelines or society position papers, that systematically address best practices pertaining to detection of DILI in these patients.

Aims: To outline best practices for detection, assessment and management of suspected acute DILI during clinical trials in adults with the cholestatic liver diseases – Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC).

Methods: This is one of the several papers developed by the IQ DILI Initiative, which is comprised of members from 16 pharmaceutical companies, in collaboration with DILI experts from academia and regulatory agencies. The contents are the result of an extensive literature review, as well as in-depth discussions among industry, regulatory and academic DILI experts, to achieve consensus recommendations on DILI-related issues occurring during clinical trials for cholestatic liver diseases.

Results: Recommended best practices are outlined pertaining to hepatic eligibility criteria, monitoring of liver tests, approach to a suspected DILI signal, and hepatic discontinuation rules.

Conclusions: This paper provides a framework for the approach to detection, assessment and management of suspected acute DILI occurring during clinical trials in adults with cholestatic liver disease.

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1 | INTRODUCTION

Cholestatic liver diseases comprise many conditions of dysfunctional bile flow and/or formation, which can lead to progressive hepatobiliary damage and its complications. While the primary pathogenic mechanisms are yet to be fully elucidated, improved knowledge of the molecular and cellular pathophysiology and immunopathogenesis of cholestatic liver diseases in recent years has led to a resurgence of interest to develop new therapies. As such, a number of drugs, some of which are novel, are currently undergoing clinical evaluation. This increase in clinical development programs for cholestatic liver diseases. has brought to light the fact that there are numerous challenges faced in detecting, assessing, and managing suspected acute drug-induced liver injury (DILI) occurring during these trials (Box 1). To start with, the literature surrounding drug DILI occurring in patients with underlying cholestatic liver diseases is scarce. There are no regulatory guidelines or society position papers that systematically address best practices pertaining to detection of DILI in these patients. Furthermore, patients with these conditions likely require different approaches to the assessment and management of suspected DILI, compared to patients with normal livers, or patients with parenchymal liver diseases such as viral hepatitis or non-alcoholic steatohepatitis (NASH). Thus, standard liver biochemical monitoring and stopping rules in the face of acute drug-associated liver injury may not be applicable to those with underlying cholestatic diseases. As there are a growing number of clinical trials assessing drugs for the treatment of cholestatic liver diseases, there is a great unmet need for consistent, evidence-based recommendations for best practices pertaining to suspected DILI in such patients. This consensus paper focuses on best practices for detection, assessment, and management of suspected acute DILI occurring during clinical trials in adults with cholestatic liver diseases.

The IQ DILI Initiative was launched in June 2016 within the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ consortium) to reach consensus and propose best practices on topics related to clinical DILI.[1] The IQ Consortium is a science-focused, not-for-profit organisation addressing scientific and technical aspects of drug development and is comprised of 38 pharmaceutical and biotechnology companies. The IQ DILI Initiative is an affiliate of the IQ Consortium, comprised of 17 IQ member companies, focused on establishing best practices for monitoring, diagnosing, managing, and preventing DILI. This publication is based on an extensive literature review, and the consensus achieved in carefully structured discussions between IQ DILI members and academic and regulatory experts. The recommendations are based on the opinions of the authors, and do not imply a regulatory guidance or mandate.

This paper will be limited to a discussion of detection, assessment and management of acute hepatocellular and cholestatic DILI in adults with Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC) without advanced liver disease (Child Pugh B, and C) who are participating in clinical trials. Due to the scarcity of data in the published literature, other types of acute DILI and chronic forms of DILI (eg, vanishing bile duct syndrome or nodular regenerative hyperplasia) will not be discussed in this paper. However, it is strongly recommended that drug developers and investigators remain mindful of these less common types of DILI that could arise during drug development. While a complete discussion of the detection, assessment and management of DILI occurring in patients with paediatric cholestatic liver diseases is beyond the scope of this paper, there are many salient features specific to these patients which will be briefly addressed. Finally, a discussion of causality assessment is beyond the scope of this publication and will not be addressed in detail. A full discussion of

Box 1 Key Challenges Faced in Detecting, Assessing, and Managing Suspected Acute Drug Induced Liver Injury (DILI) occurring During Clinical trials in Cholestatic Liver Diseases

1. The literature surrounding DILI occurring in patients with underlying cholestatic liver diseases is scarce.
2. It is unknown if patients with cholestatic liver disease have an increased susceptibility to DILI or worse outcomes when DILI occurs, compared with those with normal livers or patients with hepatocellular liver disease.
3. There are no regulatory guidelines or society position papers that systematically address monitoring and stopping criteria for patients with cholestatic liver disease who develop a hepatocellular or cholestatic DILI signal.
4. Liver biochemical monitoring and stopping rules that are utilized for patients with normal livers or patients with hepatocellular liver disease may not be applicable to those with cholestatic liver diseases.
5. The upper limit of normal for alkaline phosphatase varies among laboratories and some laboratories report separate upper limit of normal values for different sex and age groups.
6. Cholestatic DILI may be indistinguishable from progression of the underlying cholestatic liver disease both clinically as well as histologically
7. biochemical tests often fluctuate in patients with PSC possibly due to intermittent blockage of strictured bile ducts by biliary sludge or small stones confounding evaluation for DILI.
8. The natural course of PSC characteristically includes episodes of cholangitis which may mimic DILI biochemically, making detection and assignment of causality challenging.
9. The optimal approach of applying Hy's Law in clinical trials in patients with cholestatic liver disease is still a matter of debate, and clear guidelines and definitions are lacking.
10. Establishing liver biochemical test monitoring and stopping rules based solely on multiples of upper limit normal may result in inconsistent and/or incorrect evaluation of the hepatotoxicity of the candidate drug.

these topics will be the focus of subsequent papers from the IQ DILI Initiative.

2 | DEFINING THE PATTERN OF DILI IN PATIENTS WITH CHOLESTATIC LIVER DISEASE

The three predominant patterns of liver blood test elevations used to differentiate and classify the types of DILI are hepatocellular, cholestatic and mixed. The international criteria for liver toxicity, established by the Council of International Organizations of Medical Sciences (CIOMS) in 1990, defined the pattern of liver injury by using an *R* value,[2,3]

$$\text{where } R = \frac{\text{(alanine aminotransferase (ALT) /upper limit normal (ULN)}}{\text{alkaline phosphatase (ALP) /ULN}}$$

The ratio is ≥5 in acute hepatocellular injury, <2 in cholestatic liver injury, and between 2 and 5 in mixed hepatocellular-cholestatic liver injury.[2,3] However, it has been recommended that for patients with underlying liver disease and baseline abnormal hepatic biochemical indicators, *R* values derived from serum test results at the peak of acute drug-associated liver injury should be calculated using the mean baseline values obtained prior to exposure to the suspect drug, instead of the ULN.[4] This should then be compared with the R value after drug exposure. It should be emphasised that the utility of the R value in patients with underlying cholestatic liver disease has not been defined or systematically evaluated and therefore, needs to be established.

2.1 | CONSENSUS RECOMMENDATIONS 1 & 2

1. The utility of the *R* value in patients with cholestatic liver disease has not been demonstrated and therefore, needs to be established
2. If the *R* value is used to define the pattern of DILI in patients with PBC or PSC, it is recommended that the *R* value of the suspected event be compared to the baseline *R* value of the underlying disease, although the significance of a shift from the baseline value has not been assessed, and therefore, needs to be established.

3 | ARE PATIENTS WITH CHRONIC CHOLESTATIC LIVER DISEASE AT INCREASED RISK FOR DILI?

Experts in the field of DILI generally consider that patients with underlying chronic liver disease, do not appear to have an increased susceptibility for DILI compared with those patients without chronic liver disease.[5-7] However, should DILI occur, patients with chronic liver disease have an increased incidence of morbidity and mortality compared with those with healthy livers. [7-9] Of note, patients with PBC and PSC were excluded in the drug-induced liver injury network (DILIN) studies,[8,10] and thus, findings from the drug-induced liver injury network may not be applicable to patients with cholestatic liver disease. Finally, two studies noted cases of an increased likelihood of hepatotoxicity when rifampicin was given to patients with PBC to treat pruritus[11,12] compared to the incidence reported when rifampicin was given to those without underlying chronic liver disease noted in other studies.[13] These studies were not placebo-controlled and consisted of case reports or retrospective chart reviews. Thus, a definitive conclusion as to the increased risk of hepatotoxicity due to rifampicin in patients with PBC cannot be drawn.

3.1 | CONSENSUS RECOMMENDATIONS 3-6

3. It is unknown if patients with chronic cholestatic liver disease have an increased susceptibility to DILI
4. The outcome of DILI in patients with cholestatic liver disease has not been specifically studied, but until proven otherwise, it is a good practice to consider that acute DILI occurring in patients with cholestatic liver diseases, especially those with advanced liver disease, is associated with worse outcomes.
5. Studies are needed to evaluate if patients with cholestatic liver diseases are more susceptible to DILI than those with normal livers, or patients with hepatocellular liver disease.
6. Studies are needed to evaluate if DILI occurring in patients with cholestatic liver diseases is associated with worse outcomes

4 | PRIMARY BILIARY CHOLANGITIS

PBC is a chronic autoimmune cholestatic liver disease in which the small and medium-sized intrahepatic bile ducts are the target of destruction leading to cholestasis, portal inflammation, fibrosis and cirrhosis. [14,15] The diagnosis of PBC is made when two of the following are present: an elevated ALP, a positive antimitochondrial antibody (AMA) and/or consistent liver histology.[15,16] Prevalence is estimated at 1.9 to 40.2 per 100 000 people.[17] Approximately 90% are Caucasian women, and the median age at presentation is 52 years.[17-19] While the rate of disease progression may vary individually, PBC is characterised by a slow steady progression occurring over many decades.[15] With the approval of ursodeoxycholic acid in 1997, the natural history of PBC has improved and this drug remains a first line treatment for PBC.[20-23] Up to 40% of ursodeoxycholic acid-treated patients have persistently elevated ALP levels which have been associated with reduced transplant-free survival.[22,24-26] Obeticholic acid was approved in 2016 to be used in combination with ursodeoxycholic acid for those patients who have an inadequate response to ursodeoxycholic acid alone or as monotherapy for those patients intolerant to ursodeoxycholic acid 0.[27,28] Other drugs with varied mechanisms of action are currently in development with the goal of expanding treatment options, improving response rates and prolonging survival.[29-41]

5 | HEPATIC ELIGIBILITY CRITERIA FOR PATIENTS WITH PBC

As is characteristic of all cholestatic liver diseases, the degree of ALP elevation is higher than the degree of aminotransferase elevation in PBC. ALP typically ranges from 2 to approximately 10 x ULN, although ALP may be normal in the early stages of disease.[42-46] While mean ALP values most commonly range between 2-3 × ULN,[27,44,47] a recent study from Mexico comparing survival rates of patients treated with ursodeoxycholic acid compared with other treatments, reported that entry ALP prior to the start of either ursodeoxycholic acid or other drugs was 5.2 ± 3.7 × ULN and 4.0 ± 4.5 × ULN (mean ± SD) in the two groups respectively.[43] Most trials studying new medications for PBC include patients already on ursodeoxycholic acid, but have had a suboptimal response, as defined by ALP elevation or intolerance to ursodeoxycholic acid. The analysis of the global PBC study group data supported that ALP and bilirubin levels may be used as surrogate endpoints for clinical outcome prediction (liver transplantation or death).[48] As such, reduction in ALP has been used as a primary efficacy endpoint in clinical trials, and an ALP of at least >1.5× ULN is normally required for clinical trial inclusion. Reduction in ALP for PBC clinical trials would not be an appropriate surrogate endpoint in all populations or drugs that would potentially treat PBC. Reductions in ALP are likely to be predictive in patients with early-stage PBC (Rotterdam criteria) but has not been evaluated as a standalone endpoint in other populations with more advanced disease. In addition, ALP can only be used as an endpoint if the drug mechanism of action is in the pathway of ALP production.

An upper limit for ALP exclusion has typically not been specified in PBC clinical trials.[31-41] Since it is rare for patients with PBC to have an ALP >10× ULN, it seems prudent to exclude these patients from trial participation, especially in early phase trials (phase 1 and 2). Inclusion of patients with ALP elevations higher >10× ULN may be considered for later phase trials (Phase 3/4) or included for study as a subpopulation. As the ALP ULN varies among laboratories and some laboratories report different ULN for different sex and age groups, absolute values should be reported and analysed along with multiples of ULN values.

ALP may originate from tissues other than the liver, most commonly from bone.[49] Thus, gamma glutamyl transferase (GGT) and/or ALP fractionation to determine the percent derived from the liver isoenzyme versus bone or another nonliver origin, is important to determine baseline levels. For example, elevated ALP may be of bone origin in post-menopausal women who have osteoporosis and bone turnover.[50] Thus, baseline isoenzyme identification and/or GGT will prove useful during causality assessment if ALP elevations occur during the clinical trial.

Aminotransferases are often elevated, but are usually <3× ULN, and as such, some PBC clinical trials excluded patients with aminotransferases >3× ULN.[21,42,47,51-57] Since the diagnosis of PBC does not require a liver biopsy in the setting of a positive antimitochondrial antibody, an ALP >1.5× ULN and an AST ≤5 times normal,[15,58] most trials have defined aminotransferase levels >5× ULN as an exclusionary criterion.[31-41] However, some trials have no upper limit for aminotransferase exclusion criteria. Total bilirubin levels are typically normal until cirrhosis has occurred. Exclusion criteria for entrance into clinical trials located on clinicaltrials.gov have included a total bilirubin >2× ULN or total bilirubin >2 mg/dL.[31-41] Fluctuations of these liver tests are uncommon, and repeat testing at two or more different time points to determine baseline values did not appear to be done in any clinical trials.

Patients with co-incident other acute or chronic liver diseases such as hepatitis B (HBV), hepatitis C (HCV), alcoholic liver disease, NASH, PSC and autoimmune hepatitis in addition to human immunodeficiency virus (HIV), are typically excluded from PBC clinical trials. Patients with PBC/autoimmune hepatitis overlap disease have been defined as the finding of two of the following three characteristics: (a) ALT >5× ULN (b) immunoglobulin G >2× ULN and/or positive anti-smooth muscle antibodies; and (c) liver histology revealing moderate or severe periportal or periseptal inflammation.[59] It is important to remember that elevated titres of antinuclear antibodies occur in 30%-50%, and elevated titres of anti-smooth muscle antibodies have also been found in patients with PBC in the absence of overlapping autoimmune hepatitis.[60-64]

5.1 | CONSENSUS RECOMMENDATIONS 7-14

7. Clinical trials in patients with PBC who do not have advanced cirrhosis (ie Child Pugh B or C) should aim to exclude patients with the following liver test values
   a. alkaline phosphatase <1.5× upper limit normal (for lower limit eligibility)
   b. alkaline phosphatase >10× upper limit normal(for upper limit eligibility)
   c. aminotransferases >5× upper limit normal
   d. total bilirubin >1.0× ULN in the absence of Gilbert's Syndrome or haemolysis
8. Inclusion of patients outside of the above ranges may be considered for later phase trials (Phase 3 or 4) or included for study as a subpopulation
9. Absolute laboratory values should be reported and analysed along with multiples of upper limit normal values
10. Patients with other co-existing acute or chronic liver diseases should be excluded in early phase trials (Phase 1 or 2). Inclusion of patients with concomitant liver disease may be considered for later phase trials (phase 3 or 4) or for a subpopulation study.
11. Elevated alkaline phosphatase should be confirmed to be of hepatobiliary origin with a GGT and/or alkaline phosphatase isoenzyme fractionation
12. Baseline antinuclear antibody and anti-smooth muscle antibody titres, as well as immunoglobulin G levels should be established prior to study start
13. If antinuclear antibody or anti-smooth muscle antibody titres are > 1:80 or immunoglobulin G > 2 in combination with an alanine aminotransferase <5× upper limit normal a liver biopsy should be done to rule out overlap disease, and if present these

patients should be excluded. Inclusion of patients with overlap disease may be considered for later phase trials (phase 3 or 4) or for a subpopulation study.

14. Patients with history of or current evidence of decompensated liver disease (ie bleeding oesophageal varices, hepatic encephalopathy, poorly controlled ascites), prolonged international normalised ratio unable to be corrected by vitamin K, thrombocytopenia, history of liver transplantation, current placement on a liver transplant list or current Model for End-stage Liver Disease score ≥ 15 should be excluded, unless specifically studying this advanced patient population.

6 | MONITORING OF LIVER TESTS AND DILI DETECTION IN PBC CLINICAL TRIALS

Studies from the pre-ursodeoxycholic acid era demonstrated that PBC progresses slowly and steadily over many decades, without significant fluctuations in ALP or aminotransferase levels, however, as disease progresses total bilirubin may elevate.[65-69] This pattern is also seen from data from the placebo (placebo) arm of clinical trials which demonstrate that over a 12-24 month period of time liver tests remain relatively stable, with the exception of total bilirubin which shows a gradual rise over time in those trials that included patients with advanced PBC.[47,53] This finding is important as it signifies that clinically significant abrupt elevations in liver tests that occur during a PBC clinical trial should prompt increased monitoring and evaluation for potential DILI. Tables 1-3 detail algorithms for monitoring, interrupting and stopping drug for potential hepatocellular and/or cholestatic DILI in individual study subjects. Criteria for evaluation in instances of both normal and elevated baseline values of ALT are recommended.

Consensus opinion from the IQ DILI initiative recommends that patients entering trials with normal baseline ALT should initiate accelerated monitoring during the study when ALT ≥5× ULN if asymptomatic and total bilirubin is normal. The study drug should be interrupted when ALT ≥8× ULN if total bilirubin is normal or when ALT ≥3× ULN if total bilirubin ≥2× baseline or direct bilirubin >2× baseline and baseline is >0.5 mg/dL or when ALT ≥5× ULN if liver-related symptoms (eg, severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain) or an immunologic reaction (eg, rash, >5% eosinophilia).

Guidelines for assessing new elevations of ALP are also addressed in this algorithm, using multiples of elevated baseline ALP values. Consensus opinion from the IQ DILI initiative recommends that an ALP elevation of 2× baseline without a clear alternative explanation should prompt accelerated monitoring. Drug interruption should also be triggered by an ALP >2× baseline in combination with either a total bilirubin >2× baseline, a greater than doubling of DBL above the baseline measure if baseline level >0.5 mg/dL and/or new onset of liver-related symptoms, including new onset or worsening pruritus or features of an immunologic reaction. ALP should be repeated within 7-10 days to confirm the reproducibility of the initial laboratory value and the direction of change from the initial value.

If cases of suspected DILI occur in a clinical trial with no alternative causal explanation, an unblinded safety assessment should be performed by an external panel of experts and a temporary pause of the trial should be considered. An episode of suspected DILI leading to hepatic decompensation in a study subject should trigger permanent study drug discontinuation if another cause is not identified.

While clinically significant elevations of liver biochemistries are not typical for PBC progression, if it is determined that these abnormalities are due to progression of the underlying disease to cirrhosis or hepatic decompensation, it is prudent to check exposure levels of the investigational product, as a dose reduction or change in the dosing regimen may be deemed necessary to avoid toxic drug levels in liver or biliary epithelial cells and subsequent DILI. However, this approach should not be used to make decisions concerning drug interruption when there is a time delay in obtaining drug exposure data.

6.1 | CONSENSUS RECOMMENDATIONS 15-18

15. Clinically significant abrupt elevations in hepatic biochemical tests should prompt accelerated monitoring and evaluation for potential DILI as detailed in Tables 1-3
16. If cases of suspected DILI marked by isolated increases of bilirubin, especially direct bilirubin, above baseline and/or other clinical or laboratory abnormalities that point to worsening of liver function occur in a clinical trial, an unblinded safety assessment of subjects with these findings should be performed by an external advisory panel of experts. Consideration should be given to temporarily pause the trial. In assessing whether the trial should be allowed to continue, the panel should also evaluate all pertinent liver safety data connected to the drug development program. Consideration by the panel for an option to change the study protocol in order to mitigate DILI risk in the clinical trial may also be warranted.
17. An episode of DILI leading to hepatic decompensation in a study subject should trigger permanent drug discontinuation
18. When it is determined that new elevations in liver tests are due to progression of PBC to cirrhosis or hepatic decompensation, it is prudent to determine exposure levels of the investigational product, as a dose reduction or change in dosing regimen may be deemed necessary to avoid toxic drug levels and subsequent DILI.

7 | OBETICHOLIC ACID AND POTENTIAL HEPATOTOXICITY

Adherence to instructions outlined in the clinical trial protocol, as well as the prescribing regimen detailed in the approved product label to modify study drug dosing or avoid treatment altogether in the presence of defined liver abnormalities remains an important aspect

TABLE 1 Algorithm for monitoring and interrupting study drug for *Hepatocellular DILI* signals in clinical trials evaluating drugs for patients with PBC and PSC without advanced cirrhosis[a] with *Normal Baseline ALT* Values

Treatment emergent ALT	Bilirubin	Symptoms[b]	Action
ALT ≥5× ULN	Normal Gilbert's syndrome or haemolysis: No change in baseline total bilirubin	None	Blood tests should be repeated in 2-5 days [c] Follow-up for symptoms
ALT ≥8× ULN	Normal or elevated	None or present	Interrupt study drug. Blood tests should be repeated within 2-5 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver enzymes return to baseline. Drug cannot be restarted if hepatic decompensation occurred.[d]
ALT ≥3× ULN	Total bilirubin ≥2× baseline Gilbert's syndrome or haemolysis: direct bilirubin >2× baseline if baseline > 0.5 mg/dL	None or present	Interrupt study drug. Blood tests should be repeated within 2-5 days [c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]
ALT ≥5× ULN	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 2-5 days [c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]

Note: Some variance should be allowed to this algorithm to take into consideration the drug under evaluation and the stage of liver disease being studied.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

[a]Advanced Cirrhosis indicates Child Pugh B and C

[b]Liver-related symptoms (eg, severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain); Immunologic reaction (eg, rash, >5% eosinophilia); New onset of or increase of pruritus; or hepatic decompensation

[c]The specific interval between tests should also be determined based on the patient's clinical condition.

[d]The study subject will require close follow-up monitoring to exclude recurrence of liver injury after restarting the study drug.

for preventing DILI in patients with chronic liver disease.[70] This is underscored by the recent incidence of liver-related adverse events occurring in patients with PBC who were prescribed obeticholic acid (Ocaliva®)a farnesoid X receptor (FXR) agonist. Approximately 15 months after regulatory approval, a warning letter was sent to healthcare practitioners concerning 19 deaths and 11 cases of serious liver injury that occurred post-approval in patients with PBC taking obeticholic acid.[71] On February 1, 2018, the FDA concluded that most, although not all, of these patients had advanced liver disease (Child Pugh B or C) and were dosed more frequently than the recommended dose as detailed in the drug label for patients with advanced liver disease.[72,73] This resulted in a label update adding a boxed warning alerting that hepatic decompensation and failure have been reported in patients with PBC with decompensated cirrhosis or Child Pugh class B or C, who were incorrectly dosed.[28] Obeticholic acid has now been listed on livertox.nih.gov as "a suspected rare cause of clinically apparent liver injury occurring mostly in patients with pre-existing cirrhosis"0.[74] In reviewing published clinical trials of obeticholic acid for PBC, it is noted that there were discontinuations due to elevated liver tests, although the profiles of these patients were not publicly available for evaluation.[27,42,47]

While monitoring and stopping criteria were also unable to be located within these publications or supplemental appendices for review, a joint lecture from the American Association for the Study of Liver Disease (AASLD) and FDA in 2016 [75] listed ALT and/or AST >3× ULN and 2× baseline or two consecutive tests of total bilirubin >ULN and 2× baseline in the absence of biliary obstruction, as the stopping criteria for obeticholic acid clinical trials for PBC. Pooled results from three PBC placebo-controlled trials revealed that liver-related adverse events were more common in subjects receiving obeticholic acid compared with those on placebo.[76]

The mechanism of action of potential obeticholic acid hepatotoxicity is unknown.[77] A case report of a patient with Child Pugh A cirrhosis due to PBC who developed clinical and histologic cholestatic hepatitis two months after stopping a higher than recommended dose of ursodeoxycholic acid (23mg/kg) and simultaneously starting obeticholic acid has recently been reported.[78] The authors of this article postulated that this event was triggered by an increase in hydrophobic bile acids in addition to a reduction in bile flow, leading to cholestatic hepatitis. In the phase 2 obeticholic acid study in patients with PBC and an inadequate response to ursodeoxycholic acid, Hirschfield and colleagues reported jaundice

TABLE 2 Algorithm for monitoring and interrupting study drug for *Hepatocellular DILI* signals in clinical trials evaluating drugs for patients with PBC and PSC without advanced cirrhosis[a]with *Elevated baseline ALT*[b]

Treatment emergent ALT	Bilirubin	Symptoms [c]	Action
ALT ≥3× baseline or ≥300 U/L (whichever occurs first)	Normal Gilbert's syndrome or haemolysis: No change in baseline total bilirubin	None	Blood tests should be repeated in 2-5 days [d] Follow-up for symptoms
ALT ≥5× baseline or ≥500 U/L (whichever occurs first)	Normal or elevated	None or present	Interrupt study drug. Blood tests should be repeated within 2-5 days[d] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. D rug cannot be restarted if hepatic decompensation occurred. [e]
ALT ≥2× baseline or ≥300 U/L (whichever occurs first)	Total bilirubin ≥2× baseline Gilbert's syndrome or haemolysis: direct bilirubin >2× baseline if baseline > 0.5 mg/dL	None or present	Interrupt study drug. Blood tests should be repeated within 2-5 days [d] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[e]
ALT ≥2× baseline or ≥300 U/L (whichever occurs first)	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 2-5 days [d] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs. [e]

Note: Some variance should be allowed to this algorithm to take into consideration the drug under evaluation and the stage of liver disease being studied.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBL, direct bilirubin; TBL, total bilirubin; ULN, upper limit of normal.

[a]Advanced Cirrhosis indicates Child Pugh B and C

[b]Elevated baseline ALT is ALT ≥1.5× ULN.

[c]Liver-related symptoms (eg, severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain); Immunologic reaction (eg, rash, >5% eosinophilia); New onset of or increase of pruritus; or hepatic decompensation

[d]The specific interval between tests should also be determined based on the patient's clinical condition.

[e]The study subject will require close follow-up monitoring to exclude recurrence of liver injury after restarting the study drug.

in two patients.[27] While the fibrosis stage of these patients was not stated in the publication, a similar mechanism of action might be postulated as these patients were on a higher dose (50mg) of obeticholic acid then ultimately recommended for patients with PBC. The livertox.nih.com website details a single case of a woman with histologic stage 3-4 PBC who had an inadequate response to ursodeoxycholic acid at a dose of 1.2 g/d. The patient was started on obeticholic acid 5 mg daily and 3 months later developed hepatic decompensation with worsening jaundice, new onset of ascites and mild hepatic encephalopathy, 3 months after starting obeticholic acid 5 mg daily. This case included a commentary that opined that while the cause was unknown, the phenotype resembled acute-on-chronic liver failure and may be due to a dose-related incident.

Lessons can be learned from the obeticholic acid experience and applied to future PBC drug development. First, dose adjustment requirements and careful monitoring as recommended in the obeticholic acid (Ocaliva®) label must be strictly adhered to in any clinical trial being planned for combination therapy using obeticholic acid. Patients with more advanced disease should be monitored on a more frequent basis than patients in early stages of disease to evaluate for signs of hepatic decompensation. Second, this example emphasises the importance of instituting pharmacokinetic monitoring of drugs and their metabolites that undergo hepatobiliary clearance early during drug development. Third, an algorithm for dose modification and discontinuation to avoid toxic drug exposure levels needs to be established prior to the start of a clinical trial. Fourth, adherence to dose modification and discontinuation criteria in response to new or worsening liver abnormalities is a crucial aspect for preventing DILI in patients with all underlying chronic liver diseases. Finally, while it is not as yet known whether other farnesoid X receptor agonist agonists in clinical development have the same pharmacokinetic profile of obeticholic acid, it is prudent for patients with more advanced disease entering clinical trials of new farnesoid X receptor agonists or patients determined to have progressed to advanced liver disease during the course of the trial, be monitored on a more frequent basis than patients in early stages of disease to evaluate for signs of hepatic decompensation.

TABLE 3 Algorithm for monitoring and interrupting study drug for *Cholestatic DILI* signals in clinical trials evaluating drugs for patients with PBC and PSC without advanced cirrhosis[a]

Treatment emergent Alkaline phosphatase (ALP)	Bilirubin	Symptoms[b]	Action
ALP ≥2× baseline without alternative explanation	Normal or Gilbert's syndrome or haemolysis: No change in baseline total bilirubin	None	Repeat Blood tests in 7-10 days[c] Follow-up for symptoms
ALP ≥2× baseline without alternative explanation	Total bilirubin ≥2× baseline or Gilbert's syndrome or haemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	Interrupt study drug. Blood tests should be repeated within 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]
ALP ≥ 2× baseline without alternative explanation	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]
ALP ≥ 3× baseline without alternative explanation	Normal or elevated	None or present	Interrupt study drug. Blood tests should be repeated within 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurred.[d]

Note: Some variance should be allowed to this algorithm to take into consideration the drug under evaluation and the stage of liver disease being studied.

Abbreviations: ALP, Alkaline Phosphatase; ULN, upper limit of normal.

[a]Advanced Cirrhosis indicates Child Pugh B and C

[b]Liver-related symptoms (eg, severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain); Immunologic reaction (eg, rash, >5% eosinophilia); New onset of or increase of pruritus; or hepatic decompensation

[c]The specific interval between tests should also be determined based on the patient's clinical condition.

[d]The study subject will require close follow-up monitoring to exclude recurrence of liver injury after restarting the study drug.

7.1 | CONSENSUS RECOMMENDATIONS 19-21

19. Dose adjustment recommendations as stated in the obeticholic acid (Ocaliva®) product label should be followed in any clinical trial that is investigating obeticholic acid as part of a combination therapy.
20. Patients entering clinical trials utilising obeticholic acid or any of the newer farnesoid X receptor agonists who have advanced liver disease or patients determined to have progressed to advanced liver disease during the course of the trial, should be monitored on a more frequent basis to evaluate for signs of hepatic decompensation, than patients in early stages of disease.
21. To determine whether subjects with advanced liver disease have been optimally dosed with any study drug that undergoes hepatobiliary clearance, a pharmacokinetic analysis of the parent compound and its metabolites should be performed.

8 | USE OF NEW NADIR LIVER VALUES AND STOPPING RULES IN PBC CLINICAL TRIALS

While HCV, being a hepatocellular disease, and PBC, being a cholestatic disease, differ significantly, some lessons learned from HCV drug development can be applied to drug development for new PBC therapies. In particular, since it was noted that normalisation or significant reductions of ALT values occurred within the first few weeks of direct acting antiviral therapy for HCV,[79] it was recommended that this new ALT nadir value be used instead of baseline ALT levels, to evaluate potential DILI.[80-82] As such, an elevation of ALT and/or AST >5× baseline or >5× the nadir value occurring early after treatment initiation, was used to trigger drug discontinuation in some HCV trials.[79,83]

In a review of PBC clinical trials, new nadir values of liver tests achieved after treatment initiation were not utilised in DILI monitoring or stopping rules, in spite of the fact that nadir levels for ALT and

ALP were achieved and stabilised by 1-3 months of therapy.[27,42,47,51,54] Although not assessed in any trials, the degree of reduction in ALT and ALP to achieve this nadir value was approximately a mean reduction of 15% from baseline value.[27,47,51,54] Of note, this reduction is not as steep and impressive as the reduction of ALT achieved in HCV trials in response to therapy which triggered the nadir recommendation.[79,81,82] While total bilirubin levels also decrease in response to therapy, change from baseline is mild due to the fact that most subjects enter PBC trials with a total bilirubin < 2 gm/dL.[27,42,47,51,52]

Algorithms for monitoring, interrupting and stopping drug for the management of patients with PBC in clinical trials are illustrated in Tables 1-3, and are discussed in more detail below. These algorithms include rules for both hepatocellular and cholestatic DILI, and thus, include suggested values for ALT, total and direct bilirubin and ALP. Blood tests should be repeated within 2-5 days if hepatocellular DILI is suspected, and 7-10 days if cholestatic DILI is suspected. This will confirm the reproducibility of the initial laboratory value, and the direction of change from the initial value. However, the specific interval between the tests should be shortened if the patient's clinical condition warrants a quicker response by the investigator.

8.1 | CONSENSUS RECOMMENDATIONS 22-25

22. After treatment initiation, a subject's new treatment-related stable nadir levels of alkaline phosphatase and alanine aminotransferase, as opposed to the pre-treatment baseline levels, should be used as a frame of reference to monitor and assess potential DILI in the trial. Application of the new nadir value should be considered when a >50% reduction from baseline is achieved.
23. Treatment nadir of a subject's level of total bilirubin in a clinical trial is not recommended to monitor and assess potential DILI, unless specifically studying patients with advanced liver disease who enter trials with elevated total bilirubin.
24. Monitoring, interrupting and stopping rules based on multiples of upper limit normal, threshold values, baseline and nadir values of alanine aminotransferase, alkaline phosphatase, baseline values of total and/or direct bilirubin and liver-related or immunologic-related symptoms as detailed in Tables 1-3, should be followed for patients enrolled in PBC clinical trials.
25. Blood tests should be repeated within 2-5 days if hepatocellular DILI is suspected, and 7-10 days if cholestatic DILI is suspected. However, the specific interval between the tests should also be shortened if the patient's clinical condition warrants a rapid response by the investigator.

9 | SPECIAL CONSIDERATIONS FOR CAUSALITY ASSESSMENT OF POTENTIAL DILI EVENTS IN PATIENTS WITH PBC

Causality assessment in patients with PBC participating in a clinical trial can be challenging. While a full discussion is beyond the scope of this paper, a few points specific to PBC will be discussed. When elevated liver biochemistries occur during a PBC clinical trial, it is also important to rule out the onset of PBC/autoimmune hepatitis overlap syndrome. Clues that a patient may have developed an overlap syndrome includes a new rise in ALT >5× ULN, which is uncommon for PBC alone.[59,84,85] An immunoglobulin G >2× ULN and/or anti-smooth muscle antibody titre >1:80 is characteristic of overlap syndrome and these tests should be obtained for evaluation to assist in differentiating from potential DILI. As drugs are known potential triggers for idiopathic autoimmune hepatitis, it is important to be aware that DILI can also be associated with high antinuclear antibody and anti-smooth muscle antibody titres, as well as high immunoglobulin G levels.[85-89] In addition, there is also a subset of autoimmune hepatitis known as drug-induced autoimmune hepatitis, in which patients had pre-existing undiagnosed low grade disease and/or a genetic predisposition to autoimmune hepatitis which becomes overt after being triggered by a drug.[85,86] Since a considerable degree of histologic overlap exists between all of these types of autoimmune liver disease, a liver biopsy may reveal characteristics that can distinguish idiopathic autoimmune hepatitis from DILI.[90] Finally, in addition to autoimmune hepatitis, abrupt elevations of liver tests should not be attributed to underlying PBC, and other causes such as all forms of acute and chronic viral hepatitis, HBV reactivation especially when using immunomodulatory agents, alcohol use and alcoholic hepatitis, cholelithiasis, all pharmaceuticals and therapeutic agents including prescribed and over-the-counter herbal supplements, among other causes, should also be ruled out. Of course, in many cases expert opinion and/or adjudication may still be required to weigh the uncertainty of an alternative diagnosis.

9.1 | CONSENSUS RECOMMENDATIONS 26-28

26. PBC/autoimmune hepatitis overlap syndrome, as well as idiopathic autoimmune DILI should be considered as potential causes for the new onset of elevated liver biochemistries. However, it must be kept in mind that a new-onset overlap syndrome could be drug-induced.
27. A liver biopsy should be considered as part of causality assessment as it may provide clues that assist in differentiating autoimmune hepatitis from DILI. The possible need for a liver biopsy to determine causality or to assist with the clinical management of a case of concern, should be addressed in the protocol, as well as the informed consent.
28. Additional causes of clinically significant abrupt elevations in liver blood tests including, but not limited to, acute and chronic viral hepatitis (hepatitis A-E), cholelithiasis and alcohol, other drugs both prescribed and over-the-counter herbs and supplements, should be also ruled out.

10 | PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is an idiopathic, cholestatic liver disease characterised by extra and/or intra hepatic biliary tract

inflammation and destruction that can lead to end-stage liver disease and its complications including cholangiocarcinoma.[91-93] PSC is more common in men than in women with 2:1 ratio, is associated with IBD in up to 80% of cases, has a peak incidence around 40 years of age and has a prevalence estimate of up to 16.2 per 100 000 people.[17,92] Diagnosis is made when an elevated ALP is found in association with characteristic cholangiographic (eg, magnetic resonance cholangiography, endoscopic retrograde cholangiography) findings of multifocal strictures and dilatations of bile ducts, and secondary causes of sclerosing cholangitis have been excluded.[94,95] A liver biopsy is not required for diagnosis in patients with characteristic cholangiographic findings, but is useful when atypical liver tests are present in order to diagnose small duct PSC or to rule out other aetiologies, particularly overlap syndrome.[94-96]

Aetiology is unknown but likely multifactorial, and includes, but is not limited to influences related to genetic factors, the environment, immunity, gut-lymphocyte homing and toxic bile acids.[97] Higher doses of ursodeoxycholic acid at 28 to 30 mg/kg/d have been associated with an increased mortality compared with placebo.[84] Although commonly used off-label at a dose of ~ 20 mg/kg/d,[96] there has not been a definitive recommendation in society guidelines endorsing the use of ursodeoxycholic acid in the treatment for PSC,[95,96] although ursodeoxycholic acid in doses of > 28 mg/kg/day is not advised.[96] Since liver transplantation remains the only treatment option for advanced PSC when vital hepatic functions are irreversibly compromised, a surge of novel medications have more recently been undergoing clinical trials. Some novel mechanisms of actions or class of drugs that are being explored include farnesoid X receptor agonists, fibroblast growth factor19 mimetics, peroxisome proliferator-activated receptors agonists, derivatives of ursodeoxycholic acid, infliximab and monoclonal antibodies and antibiotics which may manipulate the gut microbiome and exert both antimicrobial and immunomodulatory effects.[98]

The natural history of PSC is highly variable and needs to be studied in further detail. Its course is characteristically marked by fluctuating hepatic blood tests, symptoms and bouts of cholangitis.[99-101] Thus, determining the aetiology of abrupt elevations in liver biochemistries and differentiating an episode of acute cholangitis from DILI in patients with PSC can be challenging.

11 | HEPATIC ELIGIBILITY CRITERIA FOR PATIENTS WITH PSC

Hepatic biochemical tests in PSC typically indicate cholestasis, with the most common biochemical abnormality being elevated ALP. Baseline ALP values from published clinical trials ranged from 1.5-10× ULN, with a mean ranging between 2-4× ULN.[42,84,102-111] However, ALP may be normal[112,113] or during an episode of cholangitis can be ≥10x ULN.[93,94] Inclusion criteria of ALP for eligibility into PSC treatment trials have included a lower limit ranging from 1.5-2× ULN[114-124] without specification of an upper limit for exclusion. Since levels of ALP >10× ULN rarely occur during disease progression in the absence of acute cholangitis, it is reasonable to set this as the upper limit for exclusion criteria. Confirming stability and setting an upper limit of ALP for exclusion, will likely improve diagnostic accuracy and eliminate enrolling patients with ongoing biliary complications. However, since there are no validated markers of disease activity, differentiating between a PSC flare occurring during treatment and potential cholestatic DILI remains challenging.

Repeat liver test measurements to determine the stability of baseline levels for individual study subjects in clinical trials have infrequently been done in chronic liver disease clinical trials or referenced in the literature. Nonetheless, Chalasani *et. al.* recommended to obtain two ALT measurements to determine baseline levels, and if a major difference (ie >50%) existed between the two tests, a third test was recommended to determine the degree and direction of the change.[125] As ALP often fluctuates, it is prudent to repeat this measurement to confirm stability prior to the start of study medication. Subjects in the AESOP trial, a phase 2 study testing obeticholic acid in PSC, who received placebo, experienced a mean ALP reduction of 9% from baseline which likely represented normal ALP fluctuation in PSC. This was in comparison to subjects on obeticholic acid who achieved a 31% ALP reduction from baseline after 24 weeks.[126] While obtaining serial ALP measurements to establish baseline levels has not as yet been routinely adopted, one trial required that the ALP did not fluctuate >15% in the past 3 months prior to enrolment.[127] In addition to determining the stability of the baseline level for the purposes of assessing efficacy endpoints and facilitating DILI monitoring, repeat testing of ALP prior to study start may add value to avoid enrolment of patients undergoing an episode of acute cholangitis. If values vary widely (ie, >30%), enrolment should be postponed until further screening demonstrates stable values or the aetiology is identified and corrected.

While not typically done in PSC clinical trials, as stated above, setting an upper limit of ALP level for study subject exclusion, will likely improve diagnostic accuracy, eliminate enrolling patients with ongoing biliary complications and reduce confusion between potential cholestatic DILI and an episode of cholestasis due to the natural history of PSC, during the course of the clinical trial.

Total bilirubin levels are typically normal at presentation in the majority of patients with PSC, unless they are diagnosed in an advanced stage of disease or have Gilbert's Syndrome or haemolysis. However, marked fluctuations can occur independent of disease severity due to bouts of cholestasis. Levels ranging from <1.5× ULN to <3× ULN are required for eligibility into most clinical trials, in the absence of Child Pugh B or C or liver decompensation.[104,114-124] As such, most baseline total bilirubin levels in published clinical trials of treatment for PSC have been normal or slightly abnormal.[42,84,103-108,110]

Aminotransferase levels are elevated in the majority of patients (2-5× ULN) but can also be in the normal range. However, peak aminotransferase levels are rarely above 300 U/L.[93,128,129] As opposed to the relative consistency of ALP and total bilirubin levels set for inclusion criteria among different PSC clinical trials listed on clinical trials.gov, there has been a wide variance of aminotransferase levels listed for eligibility criteria ranging from <5× ULN to <10× ULN.[95,114-124,130]

The prevalence of autoimmune hepatitis in patients with PSC ranges between approximately 2% and 17%.[92,96,131] These patients typically have aminotransferases >5× ULN, underscoring the need to have an upper limit threshold for aminotransferases for trial eligibility. It is also important to remember that, antinuclear antibody, anti-smooth muscle antibody and antineutrophil cytoplasmic antibodies are common in patients with PSC.[93,111,132,133]

Patients with other co-incident chronic liver diseases, such as HBV, HCV, alcoholic liver disease and PBC, in addition to HIV, have been excluded from PSC clinical trials. This disease specificity decreases uncertainty regarding how to interpret measured responses to study drug, as well as improves detection of suspected DILI when abrupt elevations of liver blood tests occur during the course of the trial.

Finally, as the biochemical presentation, course of disease, as well as treatment differ, immunoglobulin G4 (IgG4)-associated subtype of PSC has historically been excluded from PSC clinical trials. In addition, patients with immunoglobulin G4-associated PSC have an increased risk of autoimmune cholangitis and pancreatitis,[134] which will further confound DILI causality assessment.

11.1 | CONSENSUS RECOMMENDATIONS 29-38

29. Alkaline phosphatase >10× upper limit normal should be set as the upper limit for exclusion criteria in early phase (1 or 2) clinical trials of PSC
30. Inclusion of patients with alkaline phosphatase elevations higher > 10 x upper limit normal may be considered for later phase trials (Phase 3 or 4) or included for study as a subpopulation.
31. Absolute values should be reported and analysed along with multiples of upper limit normal
    a. Gamma glutamyl transferase and/or alkaline phosphatase fractionation should be done prior to study start
32. Two consecutive alkaline phosphatase and aminotransferase measurements should be obtained at least > 2 weeks apart during the screening period. If values vary widely (eg, >30%), enrolment should be postponed until further screening demonstrates stable values or the aetiology is identified and corrected.
33. The average of those two consecutive screening measurements plus the baseline measurement (usually Day 0) should determine baseline alkaline phosphatase and aminotransferase levels.
34. Patients with baseline elevations in total bilirubin, unless Gilbert's Syndrome or haemolysis is present, should be excluded from clinical trials of PSC, unless specifically studying patients with advanced disease (ie, Child Pugh B and C).
35. Patients with aminotransferase levels of >5× ULN should be excluded from phase 1 and 2 PSC clinical trials but may be considered for study in subpopulations or in later phase trials.
36. Patients with other co-incident acute or chronic liver diseases, such as HBV, HCV, alcoholic liver disease, PBC and autoimmune hepatitis, in addition to HIV, should be excluded from early PSC clinical trials, but may be considered for study in subpopulations or in later phase trials.
37. Immunoglobulin G4 levels should be tested at screening and patients with immunoglobulin G 4-associated PSC should be excluded. Separate studies of this patient population may be considered.
38. Titres of antinuclear antibody and anti-smooth muscle antibody should be established at baseline. Patients determined to have overlap syndrome should be excluded from phase 1 and 2 PSC clinical trials but may be considered for study in subpopulations or in later phase trials.

12 | SPECIAL CONSIDERATIONS FOR CAUSALITY ASSESSMENT OF POTENTIAL DILI EVENTS IN PATIENTS WITH PSC WITHOUT ADVANCED CIRRHOSIS (CHILD PUGH B, C)

The natural course of PSC characteristically includes episodes of cholangitis which may mimic DILI biochemically, making detection and assignment of causality challenging. Abrupt elevations of ALP, total bilirubin and/or aminotransferases alone or in combination, may reflect transient obstruction of strictured bile ducts that results from inflammation, bacterial cholangitis, sludge or choledocholithiasis.[96] Total bilirubin should be fractionated to determine the percentage derived from direct bilirubin. Aetiology of elevated ALP should be confirmed to be of liver or biliary origin with ALP isoenzymes and/or GGT. 5'-nucleotidase can also be obtained, although not as commonly used. Elevations of these liver tests should prompt evaluation for a dominant stricture with magnetic retrograde cholangiography or endoscopic retrograde cholangiography which also aids in detection of cholangiocarcinoma. The presence of fever, right upper quadrant pain and jaundice coupled with elevated inflammatory blood tests (white blood cell count and C- reactive protein) will assist in assigning causality to cholangitis.[135] Total bilirubin elevations are usually less than 15 mg/dL in cholangitis but may exceed this level with complete bile duct obstruction which can occur in PSC complicated by cholangiocarcinoma.[135]

Additional aetiologies including, but not limited to, benign or malignant neoplasms including cholangiocarcinoma, previously undiagnosed autoimmune hepatitis as well as viral and alcohol-related hepatitis, may also cause abrupt elevations in liver tests, and may need to be eliminated prior to causality being assigned to the investigational product..[93,94,99,101,136-138]

12.1 | CONSENSUS ERCOMMENDATIONS 39-41

39. Elevated total bilirubin should be fractionated to determine the percentage derived from direct bilirubin
40. Elevated alkaline phosphatase should be confirmed to be of hepatobiliary origin with a gamma glutamyl transferase and/or alkaline phosphatase isoenzyme fractionation
41. When elevations in liver tests abruptly occur, evaluation for a dominant stricture by magnetic resonance cholangiography or

endoscopic retrograde cholangiography should be considered which also aids in detection of cholangiocarcinoma.

13 | MONITORING OF LIVER BIOCHEMISTRIES AND DILI DETECTION IN PSC CLINICAL TRIALS

Monitoring and stopping rules for liver test elevations from PSC clinical trials and publications were not readily located in the public domain for review. Suggested algorithms (Tables 1-3), include monitoring and stopping rules for both hepatocellular and cholestatic DILI, and thus, include suggested values for ALP, ALT and total bilirubin. The criteria suggested for ALP were based on the requirement to be at least 1.5× ULN for inclusion into PSC trials, as well as the fact that characteristic of PSC, ALP levels often fluctuate possibly due to intermittent blockage of strictured bile ducts by biliary sludge or small stones. Thus, differentiation from potential DILI can be challenging. Consensus opinion from the IQ DILI initiative suggests that an ALP elevation of 2× baseline without a clear alternative explanation should prompt accelerated monitoring. Drug interruption/discontinuation should be triggered by an ALP >3× baseline, unless another aetiology, such as acute cholangitis has been suspected/confirmed respectively. Drug interruption should also be triggered by an ALP >2× baseline in combination with either a total bilirubin >2× baseline or DBL >2× baseline if >0.5 mg/dL or new onset of liver-related symptoms such as fatigue, nausea, new onset of or worsening or pruritus and/or right upper quadrant pain or immunologic reaction such as rash or >5% eosinophilia. Prior to initiating drug interruption, ALP should be repeated within 2-5 days to confirm the reproducibility of the initial laboratory value and the direction of change from the initial value.

There is no single definitive prognostic biomarker for measuring PSC disease progression and there is a lack of consensus over clinically relevant endpoints in PSC clinical trials. However, ALP is the most commonly utilised surrogate biomarker and as such, is typically the primary endpoint in most early phase PSC treatment trials.[114-124,139] Thus, a reduction of ALP has been utilised as an indicator of treatment response and has been noted to occur by week 12 in many trials and as early as week 4 of treatment in some.[42,104] Once this new nadir ALP value has been reached, and has been stabilised, it is recommended to use this new value, if it has decreased by more than 50%, in lieu of the baseline ALP value, to assess potential drug-induced cholestasis.

Consensus opinion from the IQ DILI initiative recommends that patients entering trials with normal baseline ALT should initiate accelerated monitoring during the study when ALT ≥5× ULN if asymptomatic and total bilirubin is normal. The study drug should be interrupted when ALT ≥8× ULN if total bilirubin is normal or when ALT ≥3× ULN if total bilirubin ≥2× baseline or direct bilirubin (DBL) >2× baseline and baseline is >0.5 mg/dL or when ALT ≥5× ULN if liver-related symptoms (eg severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain) or an immunologic reaction (eg, rash, >5% eosinophilia).

While not used as a primary endpoint, or as a surrogate marker of disease progression, an elevated ALT level may decrease and stabilise at a new level in response to therapy.[104] Thus, if a new ALT nadir level, as defined by a reduction of more than 50%, is achieved, this level, once stabilised, should be considered when evaluating stopping criteria related to potential DILI. On the other hand, since clinical trials typically exclude patients with markedly elevated total bilirubin levels, a new nadir value for total bilirubin should not be necessary when monitoring or assessing causality.

13.1 | CONSENSUS RECOMMENDATIONS 42-48

42. After treatment initiation, utilisation of a subject's new stable nadir level of alkaline phosphatase and alanine aminotransferase (if achieved), as opposed to baseline level, should be used to monitor and assess potential DILI going forward in the trial.
43. Application of the new nadir value for alkaline phosphatase and alanine aminotransferase should be considered when a > 50% reduction from baseline is achieved
44. Treatment nadir of a subject's level of total bilirubin in a clinical trial is not recommended to monitor and assess potential DILI, unless specifically studying patients with advanced liver disease who enter trials with elevated total bilirubin.
45. Monitoring and stopping rules based on multiples of upper limit normal baseline and nadir values of alkaline phosphatase and alanine aminotransferase, baseline values of total bilirubin and liver-related or immunologic-related symptoms as listed in Tables 1-3, should be followed for clinical trials of patients with PSC without decompensated cirrhosis.
46. If cases of suspected DILI occur in a clinical trial with no alternative causal explanation, an unblinded safety assessment should be performed by an external panel of experts and a temporary pause of the trial should be considered.
47. An episode of DILI resulting in hepatic decompensation should trigger permanent drug discontinuation
48. Blood tests should be repeated within 2-5 days if hepatocellular DILI is suspected, and 7-10 days if cholestatic DILI is suspected. However, the specific interval between the tests should also be based on the patient's clinical condition.

14 | CHOLESTATIC DILI

Cholestatic liver injury is responsible for ~ 20%-40% of all DILI cases, although older patients (≥60 years) may be more prone to cholestatic DILI comprising up to 61% of compiled cases.[140-142] Elevated baseline ALP due to the underlying cholestatic liver disease, makes it particularly challenging to diagnose cholestatic DILI in this patient population.

When worsening cholestasis occurs during a clinical trial of PBC or PSC, cholestatic DILI is typically indistinguishable from progression of the underlying cholestatic liver disease both clinically as well

as histologically.[143,144] The use of ALP ≥2× ULN as the threshold to identify the cholestatic pattern of liver injury[2,3] would not be applicable to patients with PBC and PSC, as an ALP of at least >1.5 ULN is already a requirement for trial eligibility. Thus, it is recommended to apply baseline values, in lieu of ULN, for ALP monitoring and stopping rules for PBC and PSC clinical trials. As such, ALP >2× baseline, unless an alternative explanation is found, should initiate increased monitoring. An ALP >3× baseline or an ALP >2× baseline occurring temporally, with either a total bilirubin elevation of >2× ULN or symptoms, in the absence of an alternative explanation should trigger drug interruption. Symptoms include: liver-related symptoms, such as: severe fatigue, nausea, right upper quadrant pain; immunologic symptoms, such as rash or > 5% eosinophilia; or other symptoms, such as new onset of or worsening of pruritus (Tables 1-3). Liver decompensation events due to DILI should trigger permanent discontinuation.

Blood tests should be repeated within 7-10 days if cholestatic DILI is suspected, in comparison to 2-5 days if hepatocellular DILI is suspected. However, the specific interval between the tests should be determined based on the patient's clinical condition. It is important to note that the onset of cholestatic DILI, while typically occurring between 2-12 weeks from start of drug, may occur after one year. In comparison, hepatocellular DILI typically occurs from 2 to 24 weeks from start of drug with occurrence unlikely after 52 weeks or sooner than 4 days after drug initiation.[145] Furthermore, time course for improvement with cholestatic injury is typically slower than for hepatocellular injury.[143] The source of the ALP elevation should be confirmed as originating from the liver or biliary tract by obtaining a GGT or by fractionating ALP and assessing any change from baseline. It should be noted that increases in GGT occur earlier and persist longer than ALP in cholestatic disorders.[146] GGT levels can be elevated due to other conditions, such as alcohol ingestion or other causes of enzyme induction.[147] As GGT will typically already have been determined to be elevated, ALP fractionation to obtain individual isoenzymes may be useful and should be measured when the aetiology of treatment emergent ALP elevations are unclear.

While blood tests typically return to baseline within 6 months after drug interruption, cholestatic DILI can lead in rare instances to vanishing bile duct syndrome 0.[148-150] Vanishing bile duct syndrome is a serious disease and may cause biliary fibrosis, cirrhosis and decompensated liver disease. Histologically, it can mimic PBC increasing the complexity of causality assessment.

15 | ADDITIONAL CONSIDERATIONS FOR CLINICAL TRIALS OF PBC AND PSC

As between 5%-10% of the population has Gilbert's Syndrome, it is likely that some patients enrolled in a cholestatic liver disease trial will also have this hereditary condition characterised by intermittent unconjugated (indirect) hyperbilirubinaemia in the absence of hepatocellular disease.[151,152] Total bilirubin levels in Gilbert's Syndrome are usually mildly elevated, but rarely greater than 4-5 mg/dL.[153,154] Gilbert's Syndrome is caused by a reduction of the level of the enzyme uridine 5'-diphospho--glucuronyl-transferase to 20-30% of its normal amount which results in impaired conjugation of bilirubin with glucuronic acid.[151] It is important to accurately identify Gilbert's Syndrome in clinical trials, especially clinical trials in cholestatic liver diseases, as misdiagnosis may result in unnecessary diagnostic testing, incorrect assignment of causality, as well as drug interruption or discontinuation. Diagnosis is confirmed by calculating the amount of conjugated bilirubin, which should be less than 20%-30% of the total bilirubin, in the absence of haemolysis.[155,156] It should be noted that the terms “direct” and “conjugated” hyperbilirubianemia, are regularly, yet incorrectly, used interchangeably. Direct bilirubin includes both the conjugated fraction, as well as delta bilirubin, which is bound to albumin, and thus, has a half-life of approximately 21 days. It is the presence of delta bilirubin that causes direct hyperbilirubinaemia to persist.[157] If the aetiology of prolonged hyperbilirubinaemia is uncertain, a breakdown of the direct bilirubin fraction to conjugated and delta bilirubin should be considered.

When hyperbilirubinaemia is due to DILI, the fraction of direct bilirubin should be measured, and is usually greater than 35%.[81] When the diagnosis is unclear, genetic testing for DNA mutations of uridine 5'-diphospho--glucuronyl-transferase should be considered.[158] Based on the consensus paper from Aithal and colleagues, an isolated elevation of total bilirubin aminotransferases even when it is predominantly direct hyperbilirubinaemia, should not be considered DILI.[4] However, this recommendation has not been supported in clinical trials and may not be applicable to patients with underlying cholestatic liver disease, especially those with advanced cirrhosis who typically have an altered AST to ALT ratio >1.0, instead of the normal ratio of 0.8, [159] and thus, do not manifest the same degree of ALT elevation expected to occur with DILI. In fact, consensus opinion from IQ DILI recommends to closely monitor any persistent isolated elevations in direct bilirubin in patients with cholestatic liver disease, as this may be a sign of DILI, especially in patients with underlying synthetic function impairment.

Patients with cholestatic disease are at risk for fat soluble vitamin deficiencies.[160,161] This is particularly important when evaluating the aetiology of a prolonged international normalised ratio (INR) during a PBC or PSC clinical trial, as this may indicate disease progression, DILI, or a vitamin K deficiency. It is recommended that a repeat INR value should be done within 2-5 days to confirm the value and determine trajectory and parenteral vitamin K supplementation should be attempted to correct this abnormality prior to assigning causality, unless it has been determined that more immediate evaluation such as liver transplantation is needed.

Patients with chronic HBV, as determined by HBsAg positivity, are normally excluded from PSC clinical trials in order to decrease uncertainty surrounding the interpretation of measured responses to the study drug. In addition, HBV reactivation can occur during a clinical trial, leading to elevated liver biochemistries, making differentiation from DILI a challenge. Individuals without HBV serological markers indicating resolved HBV infection (HBsAg negative, undetectable HBV DNA and HBcAb positive) can still harbour HBV DNA in the form of covalently closed circular (ccc) DNA which remains in

hepatocytes.[162] This can occur independent of the HBsAb status.[163] Thus, HBV could be reactivated when the immune system is suppressed by immunomodulatory therapy.[164] Exclusion of individuals with isolated HBcAb positivity (without elevated aminotransferases, HBV DNA or other serologic markers) into PSC trials evaluating immunomodulatory therapy, or excluding those who are already on immunomodulatory therapy for associated inflammatory bowel disease or another indication, should be considered. If it is decided to include such patients, HBV DNA should be obtained to eliminate reactivation of HBV when evaluating the aetiology of liver test abnormalities as part of the causality assessment for potential DILI.

Most patients in clinical trials of new medications for PBC and PSC will continue treatment with ursodeoxycholic acid (on label for PBC and off label for some patients with PSC) unless they are intolerant or become noncompliant. Noncompliance to ursodeoxycholic acid, (whether secondary to intolerance or some other reason) can lead to abrupt elevations of liver tests that can mimic either hepatocellular or cholestatic DILI. Thus, it is important to inquire about adherence to ursodeoxycholic acid as part of causality assessment. While assessment of adherence to ursodeoxycholic acid by performing a pill count would not be feasible unless ursodeoxycholic acid was administered as a study medication as part of the trial, adherence to study investigational product can typically be determined by pill count or medication levels.

Finally, while patients with early cirrhosis are often included in PBC and PSC clinical trials, patients with evidence of decompensation (eg, bleeding oesophageal varices, portal hypertension, hepatic encephalopathy, ascites) are excluded. In addition to the fact that endpoints to assess efficacy may differ (transplant and death), these patients may have additional risks for increased morbidity and mortality should a DILI event occur. The effect of DILI in patients with compensated versus decompensated cirrhosis has not been specifically examined in the clinical trial setting.

15.1 | CONSENSUS RECOMMENDATIONS 49-57

49. Diagnosis of Gilbert's Syndrome should be determined by calculating the proportion of conjugated bilirubin which should be less than 20%-30% of the total bilirubin. Genetic testing for DNA mutations of uridine 5'-diphospho--glucuronyl-transferase should be considered for definitive confirmation, especially when total bilirubin elevations occur in combination with elevated ALP and aminotransferases.
50. If the aetiology of prolonged hyperbilirubinaemia is unclear, a breakdown of the direct bilirubin fraction to conjugated and delta bilirubin should be considered
51. Persistent isolated elevations of direct bilirubin in patients with cholestatic liver disease, should be closely monitored, as this may be a sign of DILI, especially in patients with underlying synthetic function impairment.
52. If international normalised ratio is prolonged, a repeat should be done within 2-5 days to confirm prolongation and to determine its trajectory
53. Vitamin K supplementation should be attempted to correct prolonged international normalised ratio prior to assigning causality, unless it has been determined that more immediate measures, such as liver transplantation are required.
54. If enrolling subjects with isolated hepatitis B core antibody positivity in trials evaluating an immunomodulatory therapy or in trials where patients are already treated with an immunomodulatory agent for another indication, hepatitis B viral DNA should be obtained when abrupt elevations of liver tests occur to rule out the possibility of hepatitis B reactivation as part of causality assessment for potential DILI.
55. Non-adherence with ursodeoxycholic acid should be included in causality assessment during evaluation of abrupt elevations in liver biochemistries
56. Investigational product drug levels and pill counts, when applicable, should be considered as part of a DILI causality assessment
57. Patients with decompensated cirrhosis should be studied in separate clinical trials

16 | ALGORITHM FOR MONITORING AND MANAGEMENT OF POSSIBLE HEPATOCELLULAR OR CHOLESTATIC DILI IN PBC AND PSC CLINICAL TRIALS IN PATIENTS WITH NORMAL OR ELEVATED BASELINE ALT

Hy's law identifies hepatotoxic drugs with a potential to cause idiosyncratic severe hepatocellular liver injury.[7,165,166] In patients without underlying liver disease, a Hy's law case is defined by (a) ALT elevation ≥3× ULN; (b) total bilirubin elevation ≥2× ULN; (c) no initial finding of cholestasis (elevated ALP); and (d) no competing aetiology to explain these liver elevations. In addition, the drug should show a higher incidence of ALT ≥3× ULN compared to the control drug or placebo.[7,165,166] These criteria may not apply to patients who have an underlying cholestatic liver disease, since ALT and total bilirubin may be elevated at baseline and when ALT and total bilirubin rise further during the course of a clinical trial, the respective elevations may be related to the disease rather than DILI. Establishing liver-related stopping rules based solely on multiples of ULN may result in inconsistent and/or incorrect evaluation of the hepatotoxicity of the candidate drug. As such, the criteria of Hy's law cases listed above may not simply be applied in these situations and may not carry its predictive value. Using the baseline ALT value or new nadir level and a combination of multiples of ULN, in conjunction with an elevated bilirubin, may lead to a more accurate assessment. The optimal approach of applying Hy's Law in clinical trials in patients with cholestatic liver disease is still a matter of debate, and clear guidelines and definitions are lacking. Regulatory guidance for DILI monitoring and detection attempts to address this issue by recommending using an ALT threshold value of >2× baseline to trigger close observation and workup for competing aetiologies in patients who have elevated aminotransferase levels at study entrance.[167] However, this

Box 2 Executive Summary

Top Ten Consensus Recommendations for Detection, Assessment and Management of Suspected Acute Drug Induced Liver Injury Occurring During Clinical Trials in Adults with Chronic Cholestatic Liver Disease

1. When assessing patients with PBC and PSC for clinical trial eligibility, absolute liver biochemical test values should be reported and analyzed along with multiples of upper limit of normal values.
2. In patients with PSC, two consecutive alkaline phosphatase and aminotransferase measurements should be obtained at least >2 weeks apart during the screening period. If values vary widely (eg, >30%), enrollment should be postponed until further screening demonstrates stable values, or the etiology is identified and corrected.
3. After treatment initiation, a subject's new treatment-related stable nadir level of alkaline phosphatase and/or alanine aminotransferase, as opposed to the pre-treatment baseline level, should be used as a frame of reference to monitor and assess potential DILI. Application of the new nadir value should be considered when a >50% reduction from baseline is achieved.
4. Monitoring and stopping rules based on multiples of upper limit normal, baseline and nadir values of alkaline phosphatase and alanine aminotransferase, baseline values of total and direct bilirubin, and liver-related or immunologic-related symptoms should be followed for clinical trials of patients with PBC and PSC.
5. The optimal approach of applying Hy's Law in clinical trials in patients with cholestatic liver disease is still a matter of debate, and clear guidelines and definitions are lacking. However, using the baseline ALT value or treatment-related new nadir level and a combination of multiples of ULN, in conjunction with an elevated bilirubin may lead to a more accurate assessment.
6. In patients with PBC, PBC/autoimmune hepatitis overlap syndrome, as well as idiopathic autoimmune DILI should be considered as potential causes of a new onset of elevated liver biochemistries.
7. When it is determined that new elevations in liver tests are due to progression of cholestatic liver disease to cirrhosis, it is prudent to determine exposure levels of the investigational product, as a dose reduction or change in dosing regimen may be deemed necessary to avoid toxic drug levels and subsequent DILI.
8. Patients entering clinical trials utilizing obeticholic acid or any of the newer farnesoid X receptor agonists, who have advanced liver disease or patients determined to have progressed to advanced liver disease during the course of the trial, should be monitored on a more frequent basis to evaluate for signs of hepatic decompensation.
9. If cases of suspected DILI marked by isolated increases of bilirubin, especially direct bilirubin, above baseline and/or other clinical or laboratory abnormalities that indicate worsening liver function occur, or have no alternative causal explanation an unblinded safety assessment of subjects with these findings should be performed by an external advisory panel. A temporary trial pause should be considered. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
10. An episode of DILI resulting in hepatic decompensation should trigger permanent drug discontinuation.

guidance does not specifically address monitoring and stopping criteria for patients with cholestatic liver disease or for patients being evaluated for cholestatic DILI.

Tables 1-3, outline a detailed approach for monitoring and interrupting study drug, in clinical trials for patients with PBC and PSC who develop either hepatocellular or cholestatic DILI signals and for those with either normal or elevated baseline ALT levels.

Box 2 provides an Executive Summary in addition to listing the top 10 recommendations.

16.1 | CONSENSUS RECOMMENDATIONS 58

58. In clinical trials of patients with underlying cholestatic liver disease, using the baseline ALT value or new nadir level and a combination of multiples of ULN, in conjunction with an elevated bilirubin, may lead to a more accurate assesment of drugs with hepatotoxic potential to cause idiosyncratic severe hepatocellular liver injury, as opposed to applying the current criteria for Hy's law.

17 | PAEDIATRIC CHOLESTATIC LIVER DISEASE

A comprehensive review of assessment and monitoring of DILI in paediatric cholestatic liver diseases is beyond the scope of this paper. There is great interest in developing novel therapies for paediatric cholestatic liver diseases, many of which have an urgent unmet medical need. As such, clinical trials for many of these diseases with varied pharmacologic interventions are ongoing and more are under consideration.[168] A full discussion of this topic will be the focus of a subsequent paper from the IQ DILI Initiative. However, a few salient points will be mentioned. Significant limitations on the existing natural history data, include lack of information surrounding the range and fluctuations of common liver biochemical tests over short periods of time with these conditions. These shortcomings make recommendations about DILI monitoring and intervention in paediatric cholestatic liver diseases difficult. Notably, biochemical criteria of hepatotoxicity in adults with cholestatic disease may not apply to paediatric populations due to development-related differences in

the normal ranges of common liver tests including total bilirubin, aminotransferases, and ALP from early infancy through the pubertal growth spurt. In addition, certain hereditary cholestatic liver diseases in infants and children are not associated with the characteristic rise in GGT that are seen in PBC or PSC and cannot be relied upon as a marker of cholestatic injury.[169] During growth in normal paediatric study subjects, ALP levels are affected by fluctuations of the enzyme derived from bone. Changes of ALP in paediatric patients are also typically observed with vitamin D deficiency. Nutritional problems including fat soluble vitamin deficiency are very common and may be difficult to completely correct in paediatric cholestatic disease.[170] The clinical and biochemical course of the varied monogenic defects in bile secretion machinery that are uniquely seen in children are quite distinct from each other and thus need to be considered individually. As such, DILI monitoring and study drug stopping criteria designed for adult cholestatic liver diseases cannot simply be applied to paediatric cholestatic liver diseases. The ontogeny of intrahepatic enzymes and transporters also factor into the biochemical phenotype of infantile and early childhood paediatric cholestatic liver disease, another factor which needs to be considered in the development of guidelines for these study populations.

18 | CONCLUSION

The number of drug development programs for cholestatic liver disease, particularly PBC and PSC, has grown considerably over the last few years. Patients with these diseases often require different approaches to suspected DILI detection, assessment and management. compared to patients with healthy livers or patients with parenchymal liver disease. This paper highlights the challenges faced and provides consensus recommendations for best practices on this topic based on collaborative work of the IQ DILI initiative and DILI experts from academia, and the Food and Drug Administration. However, there are still many gaps to fill, and questions to be answered, underscoring the need for further research in this important and complex area.

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REFERENCES

1. International Consortium for Innovation & Quality in Pharmaceutical Development DILI (IQ DILI). Iq dili initiative. www.iqdili.org. Accessed February 2, 2018.
2. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990;11:272-276.
3. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs–ii. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993;46:1331-1336.
4. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89:806-815.
5. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology*. 2004;126:1287-1292.
6. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology*. 2007;46:1453-1463.
7. Zimmerman HJ. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*, 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1999.
8. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the dilin prospective study. *Gastroenterology*. 2015;148:1340-1352; e1347
9. Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using controlled clinical trials to learn more about acute drug-induced liver injury. *Hepatology*. 2008;48:1680-1689.

10. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the united states. *Gastroenterology*. 2008;135:1924-1934; e1924.
11. Bachs L, Pares A, Elena M, Piera C, Rodes J. Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology*. 1992;102:2077-2080.
12. Prince MI, Burt AD, Jones DE. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut*. 2002;50:436-439.
13. Cascio A, Scarlata F, Giordano S, Antinori S, Colomba C, Titone L. Treatment of human brucellosis with rifampin plus minocycline. *J Chemother*. 2003;15:248-252.
14. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med*. 2005;353:1261-1273.
15. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology*. 2009;50:291-308.
16. Silveira MG, Brunt EM, Heathcote J, Gores GJ, Lindor KD, Mayo MJ. American association for the study of liver diseases endpoints conference: Design and endpoints for clinical trials in primary biliary cirrhosis. *Hepatology*. 2010;52:349-359.
17. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol*. 2012;56:1181-1188.
18. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet*. 2015;386:1565-1575.
19. Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. *Lancet*. 2011;377:1600-1609.
20. Corpechot C, Carrat F, Poupon R, Poupon RE. Primary biliary cirrhosis: Incidence and predictive factors of cirrhosis development in ursodiol-treated patients. *Gastroenterology*. 2002;122:652-658.
21. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology*. 1997;113:884-890.
22. Pratt DS. Primary biliary cholangitis–a new name and a new treatment. *N Engl J Med*. 2016;375(7):685-687.
23. U.S. Food & Drug Administration (FDA). Urso package; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020675s017lbl.pdf. Accessed October 30, 2019.
24. Kuiper EMM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology*. 2009;136:1281-1287.
25. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology*. 2006;130:715-720.
26. Corpechot C, Abenavoli L, Rabahi N, ,et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology*. 2008;48:871-877.
27. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*. 2015;148:751-761; e758
28. U.S. Food & Drug Administration (FDA). Ocaliva package insert; 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207999s000lbl.pdf. Accessed October 30, 2019.
29. Dyson JK, Hirschfield GM, Adams DH, et al. Novel therapeutic targets in primary biliary cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2015;12:147-158.
30. Fuchs CD, Halilbasic E, Trauner M. Novel treatments targeting metabolic and signaling mechanisms in primary biliary cholangitis. *Clin Liver Dis*. 2017;9:43-47.
31. U.S. National Institute of Health (NIH). Mesenchymal stem cell transplantation for refractory primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT03668145. Accessed August 1, 2019.
32. U.S. National Institute of Health (NIH). Study of oca evaluating pharmacokinetics and safety in patients with pbc and hepatic impairment. https://ClinicalTrials.gov/show/NCT03633227. Accessed August 1, 2019.
33. U.S. National Institute of Health (NIH). Enhance: Seladelpar in subjects with primary biliary cholangitis (pbc) and an inadequate response to or an intolerance to ursodeoxycholic acid (udca). https://ClinicalTrials.gov/show/NCT03602560. Accessed August 1, 2019.
34. U.S. National Institute of Health (NIH). Non-comparative study of bcd-085 in combination with udca in patients with primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT03476993. Accessed August 1, 2019.
35. U.S. National Institute of Health (NIH). A study to assess the safety, tolerability, pharmacokinetics and efficacy of edp-305 in subjects with primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT03394924. Accessed August 1, 2019.
36. U.S. National Institute of Health (NIH). A trial of 18–22mg/kg/d ursodeoxycholic in refractory primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT03345589. Accessed August 1, 2019.
37. U.S. National Institute of Health (NIH). Seladelpar in subjects with primary biliary cholangitis (pbc). https://ClinicalTrials.gov/show/NCT03301506. Accessed August 1, 2019.
38. U.S. National Institute of Health (NIH). Safety, tolerability, and efficacy of etrasimod (apd334) in patients with primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT03155932. Accessed August 1, 2019.
39. U.S. National Institute of Health (NIH). A study to evaluate safety, tolerability and efficacy of saroglitazar magnesium in patients with primary biliary cholangitis (epics). https://ClinicalTrials.gov/show/NCT03112681. Accessed August 1, 2019.
40. U.S. National Institute of Health (NIH). Dose response study of gsk2330672 for the treatment of pruritus in patients with primary biliary cholangitis. https://ClinicalTrials.gov/show/NCT02966834. Accessed August 1, 2019.
41. U.S. National Institute of Health (NIH). Use of bezafibrate in patients with primary biliary cirrhosis to archive complete biochemical response in non-responders. https://ClinicalTrials.gov/show/NCT02937012. Accessed August 1, 2019.
42. Kowdley KV, Luketic V, Chapman R, et al. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis. *Hepatology*. 2018;67:1890-1902.
43. Melchor-Mendoza YK, Martinez-Benitez B, Mina-Hawat A, Rodriguez-Leal G, Duque X, Moran-Villota S. Ursodeoxycholic acid therapy in patients with primary biliary cholangitis with limited liver transplantation availability. *Ann Hepatol*. 2017;16:430-435.
44. Murillo Perez CF, Goet JC, Lammers WJ, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: a changing natural history. *Hepatology*. 2018;67:1920-1930.
45. Prince MI, Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: Clinical features, prognosis, and symptom progression in a large population based cohort. *Gut*. 2004;53:865-870.
46. Yang J, Yu Y-L, Jin Y, Zhang Y, Zheng C-Q. Clinical characteristics of drug-induced liver injury and primary biliary cirrhosis. *World J Gastroenterol*. 2016;22:7579-7586.
47. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375:631-643.
48. Lammers WJ, vanBuuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: An international follow-up study. *Gastroenterology*. 2014;147:1338-1349; e1335; quiz e1315
49. Cleeve HJW. Origin of an elevated plasma alkaline phosphatase activity in non-jaundiced patients. *Ann Clin Biochem*. 1978;15:86-90.

50. Mukaiyama K, Kamimura M, Uchiyama S, Ikegami S, Nakamura Y, Kato H. Elevation of serum alkaline phosphatase (alp) level in postmenopausal women is caused by high bone turnover. *Aging Clin Exp Res*. 2015;27:413-418.
51. Angulo P, Dickson ERolland, Therneau TM, et al. Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomized trial. *J Hepatol*. 1999;30:830-835.
52. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: Biochemical response to treatment and prediction of long-term outcome. *J Hepatol*. 2011;55:1361-1367.
53. Heathcote EJ, Cauch-Dudek K, Walker V, et al. The canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology*. 1994;19:1149-1156.
54. Oka H, Toda G, Ikeda Y, et al. A multi-center double-blind controlled trial of ursodeoxycholic acid for primary biliary cirrhosis. *Gastroenterol Jpn*. 1990;25:774-780.
55. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. Udca-pbc study group. *N Engl J Med*. 1991;324:1548-1554.
56. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The udca-pbc study group. *N Engl J Med*. 1994;330:1342-1347.
57. Vuoristo M, Fäarkkilä M, Karvonen A-L, et al. A placebo-controlled trial of primary biliary cirrhosis treatment with colchicine and ursodeoxycholic acid. *Gastroenterology*. 1995;108:1470-1478.
58. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis?*Clin Gastroenterol Hepatol*. 2003;1:89-95.
59. Chazouilleres O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatology*. 1998;28:296-301.
60. Zeman MV, Hirschfield GM. Autoantibodies and liver disease: uses and abuses. *Can J Gastroenterol*. 2010;24:225-231.
61. Muratori L, Cassani F, Pappas G, ,et al. The hepatitic/cholestatic "overlap" syndrome: An italian experience. *Autoimmunity*. 2002;35:565-568.
62. Lleo A, Shimoda S, Ishibashi H, Gershwin ME. Primary biliary cirrhosis and autoimmune hepatitis: apotopes and epitopes. *J Gastroenterol*. 2011;46(Suppl 1):29-38.
63. Yamagiwa S, Kamimura H, Takamura M, Aoyagi Y. Autoantibodies in primary biliary cirrhosis: Recent progress in research on the pathogenetic and clinical significance. *World J Gastroenterol*. 2014;20:2606-2612.
64. Alvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: Review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31:929-938.
65. Christensen E, Crowe J, Doniach D, et al. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. *Gastroenterology*. 1980;78:236-246.
66. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: Model for decision making. *Hepatology*. 1989;10:1-7.
67. Klion F, Fabry T, Palmer M, Schaffner F. Progression of primary biliary cirrhosis: Using the mayo model in a group of patients with known end point. *Gastroenterology*. 1992;102:310-313.
68. Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. *N Engl J Med*. 1983;308:1-7.
69. Sasaki H, Inoue K, Higuchi K, et al. Primary biliary cirrhosis in Japan: national survey by the subcommittee on autoimmune hepatitis. *Gastroenterol Jpn*. 1985;20:476-485.
70. Lewis JH, Stine JG. Review article: prescribing medications in patients with cirrhosis - a practical guide. *Aliment Pharmacol Ther*. 2013;37:1132-1156.
71. Administration USFD. Fda drug safety communication: Fda warns about serious liver injury with ocaliva (obeticholic acid) for rare chronic liver disease; 2017.
72. Aschenbrenner DS. Excessive dosing of obeticholic acid may increase risk of liver damage. *Am J Nurs*. 2018;118:46.
73. Administration USFD.Fda adds boxed warning to highlight correct dosing of ocaliva (obeticholic acid) for patients with a rare chronic liver disease; 2018.
74. U.S. National Institute of Health (NIH). Liver tox: Clinical and research information on drug-induced liver injury; 2018. https://livertox.nlm.nih.gov/. Accessed August 1, 2019.
75. Vierling J.Can study protocols protect patients with liver disease from serious dili?. FDA/critical path annual drug induced liver injury conference XVI. Hyattsville, MD; 2016.
76. Gastrointestinal Drug Advisory Committee (GIDAC). Gastrointestinal Drug Advisory Committee (GIDAC) Meeting 2016; Silver Spring, MD.
77. U.S. National Institute of Health (NIH). Liver tox: Clinical and researh information on drug-induced liver injury - obeticholic acid. https://livertox.nih.gov/ObeticholicAcid.htm. Accessed August 1, 2019.
78. Quigley G, Al Ani M, Nadir A. Occurrence of jaundice following simultaneous ursodeoxycholic acid cessation and obeticholic acid initiation. *Dig Dis Sci*. 2018;63:529-532.
79. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated hcv genotype 1 infection. *N Engl J Med*. 2014;370:1889-1898.
80. Avigan MI, Bjornsson ES, Pasanen M, et al. Liver safety assessment: required data elements and best practices for data collection and standardization in clinical trials. *Drug Saf*. 2014;37(Suppl 1):S19–S31.
81. Kullak-Ublick GA, Merz M, Griffel L, Kaplowitz N, Watkins PB. Liver safety assessment in special populations (hepatitis b, c, and oncology trials). *Drug Saf*. 2014;37(Suppl 1):S57-62.
82. Merz M, Lee KR, Kullak-Ublick GA, Brueckner A, Watkins PB. Methodology to assess clinical liver safety data. *Drug Saf*. 2014;37(Suppl 1):S33-45.
83. Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for hcv in patients coinfected with hiv-1. *N Engl J Med*. 2015;373:705-713.
84. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology*. 2009;50:808-814.
85. Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. *Clin Liver Dis*. 2002;6:755-774.
86. Castiella A, Zapata E, Lucena MI, Andrade RJ. Drug-induced autoimmune liver disease: a diagnostic dilemma of an increasingly reported disease. *World J Hepatol*. 2014;6:160-168.
87. Björnsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology*. 2010;51:2040-2048.
88. Weiler-Normann C, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. *J Hepatol*. 2011;55:747-749.
89. DeLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. *Semin Liver Dis*. 2014;34:194-204.
90. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. *Hepatology*. 2011;54:931-939.
91. Goldberg DS, Levy C, Yimam K, et al. Primary sclerosing cholangitis is not rare among blacks in a multicenter north american consortium. *Clin Gastroenterol Hepatol*. 2018;16:591-593.
92. Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet*. 2013;382:1587-1599.
93. Lee YM, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med*. 1995;332:924-933.

94. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010;51: 660-678.
95. European Association for the Study of the Liver (EASL). Easl clinical practice guidelines: Management of cholestatic liver diseases. *J Hepatol*. 2009;51:237-267.
96. Lindor KD, Kowdley KV, Harrison ME. Acg clinical guideline: primary sclerosing cholangitis. *Am J Gastroenterol*. 2015;110:646-659; quiz 660.
97. Pollheimer MJ, Halilbasic E, Fickert P, Trauner M. Pathogenesis of primary sclerosing cholangitis. *Best Pract Res Clin Gastroenterol*. 2011;25:727-739.
98. Rodriguez EA, Carey EJ, Lindor KD. Emerging treatments for primary sclerosing cholangitis. *Expert Rev Gastroenterol Hepatol*. 2017;11:451-459.
99. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 swedish patients with primary sclerosing cholangitis. *Gut*. 1996;38:610-615.
100. Olsson R, Broome U, Danielsson A, et al. Spontaneous course of symptoms in primary sclerosing cholangitis: Relationships with biochemical and histological features. *Hepatogastroenterology*. 1999;46:136-141.
101. Tischendorf JJ, Hecker H, Kruger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. *Am J Gastroenterol*. 2007;102:107-114.
102. Aadland E, Schrumpf E, Fausa O, et al. Primary sclerosing cholangitis: a long-term follow-up study. *Scand J Gastroenterol*. 1987;22:655-664.
103. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology*. 1992;16:707-714.
104. Fickert P, Hirschfield GM, Denk G, et al. Norursodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol*. 2017;67:549-558.
105. Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology*. 2001;121:900-907.
106. Muir A, Goodman Z, Levy C, et al. Efficacy and safety of simtuzumab for the treatment of primary sclerosing cholangitis: Results of a phase 2b, dose-ranging, randomized, placebo-controlled trial. *J Hepatol*. 2017;66:S73.
107. Olsson R, Boberg KM, Schaffalitsky de Muckadell O, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology*. 2005;129:1464-1472.
108. Silveira MG, Torok NJ, Gossard AA, et al. Minocycline in the treatment of patients with primary sclerosing cholangitis: results of a pilot study. *Am J Gastroenterol*. 2009;104:83-88.
109. Steele IL, Levy C, Lindor KD. Primary sclerosing cholangitis–approach to diagnosis. *MedGenMed*. 2007;9:20-20.
110. Stiehl A, Walker S, Stiehl L, Rudolph G, Hofmann WJ, Theilmann L. Theilmann L. Effect of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3-year pilot study with a placebo-controlled study period. *J Hepatol*. 1994;20:57-64.
111. Wiesner RH, Grambsch PM, Dickson ER, et al. Primary sclerosing cholangitis: Natural history, prognostic factors and survival analysis. *Hepatology*. 1989;10:430-436.
112. Balasubramaniam K, Wiesner RH, LaRusso NF. Primary sclerosing cholangitis with normal serum alkaline phosphatase activity. *Gastroenterology*. 1988;95:1395-1398.
113. Clements D, Rhodes JM, Elias E. Severe bile duct lesions without biochemical evidence of cholestasis in a case of sclerosing cholangitis. *J Hepatol*. 1986;3:72-74.
114. U.S. National Institute of Health (NIH). A research study to evaluate safety and efficacy of dur-928 in subjects with primary sclerosing cholangitis (psc). https://ClinicalTrials.gov/show/NCT03394781. Accessed August 1, 2019.
115. U.S. National Institute of Health (NIH). Safety, tolerability, and efficacy of gs-9674 in adults with primary sclerosing cholangitis without cirrhosis. https://ClinicalTrials.gov/show/NCT02943460. Accessed August 1, 2019.
116. U.S. National Institute of Health (NIH). Phase 2 study of ngm282 in patients with primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT02704364. Accessed August 1, 2019.
117. U.S. National Institute of Health (NIH). Perseus: Preliminary efficacy and safety of cenicriviroc in adult participants with primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT02653625. Accessed August 1, 2019.
118. U.S. National Institute of Health (NIH). A trial of btt1023 in patients with primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT02239211. Accessed August 1, 2019.
119. U.S. National Institute of Health (NIH). Obeticholic acid (oca) in primary sclerosing cholangitis (psc). https://ClinicalTrials.gov/show/NCT02177136. Accessed August 1, 2019.
120. U.S. National Institute of Health (NIH). Primary sclerosing cholangitis with oral vancomycin by the study of its antimicrobial and immunomodulating effects. https://ClinicalTrials.gov/show/NCT01802073. Accessed August 1, 2019.
121. U.S. National Institute of Health (NIH). Norursodeoxycholic acid in the treatment of primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT01755507. Accessed August 1, 2019.
122. U.S. National Institute of Health (NIH). Mitomycin c therapy for patients with primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT01688024. Accessed August 1, 2019.
123. U.S. National Institute of Health (NIH). Simtuzumab (gs-6624) in the prevention of progression of liver fibrosis in subjects with primary sclerosing cholangitis (psc). https://ClinicalTrials.gov/show/NCT01672853. Accessed August 1, 2019.
124. U.S. National Institute of Health (NIH). Safety and efficacy study of ursodeoxycholic acid therapy in pediatric primary sclerosing cholangitis. https://ClinicalTrials.gov/show/NCT01088607. Accessed August 1, 2019.
125. Chalasani N, Regev A. Drug-induced liver injury in patients with preexisting chronic liver disease in drug development: How to identify and manage?*Gastroenterology*. 2016;151:1046-1051.
126. Larusso NF, Bowlus CL, Levy C, et al. Pc.01.8 the aesop trial: a randomized, double-blind, placebo-controlled, phase 2 study of obeticholic acid in patients with primary sclerosing cholangitis. *Dig Liver Dis*. 2018;50:e67.
127. U.S. National Institute of Health (NIH). Perseus. https://clinicaltrials.gov/ct2/results?cond=Perseus&term=&cntry=&state=&city=&dist=&Search=Search. Accessed August 1, 2019.
128. Kowdley KV. Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis. 2018; https://www.uptodate.com/contents/primary-sclerosing-cholangitis-in-adults-clinical-manifestations-anddiagnosis?search=psc&source=search_result&selectedTitle=1~103&usage_type=default&display_rank=1. Accessed August 1, 2019.
129. Toy E, Balasubramanian S, Selmi C, Li CS, Bowlus CL. The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. *Gastroenterology*. 2011;11:83.
130. Clinicaltrials.Gov. 2017. https://clinicaltrials.gov/. Accessed January 2019.
131. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of mr cholangiopancreatography. *Radiology*. 2010;256:387-396.
132. Angulo P, Peter JB, Gershwin ME, et al. Serum autoantibodies in patients with primary sclerosing cholangitis. *J Hepatol*. 2000;32:182-187.

133. Seibold F, Weber P, Klein R, Berg PA, Wiedmann KH. Clinical significance of antibodies against neutrophils in patients with inflammatory bowel disease and primary sclerosing cholangitis. *Gut*. 1992;33:657-662.
134. Mendes FD, Jorgensen R, Keach J, et al. Elevated serum igg4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 2006;101:2070-2075.
135. Mosler P. Diagnosis and management of acute cholangitis. *Curr Gastroenterol Rep*. 2011;13:166-172.
136. Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. *Hepatology*. 2006;44:1063-1074.
137. Chapman RW, Arborgh BA, Rhodes JM, et al. Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. *Gut*. 1980;21:870-877.
138. Trauner M, Halilbasic E, Kazemi-Shirazi L, et al. Therapeutic role of bile acids and nuclear receptor agonists in fibrosing cholangiopathies. *Dig Dis*. 2014;32:631-636.
139. Ponsioen CY, Lindor KD, Mehta R, Dimick-Santos L. Design and endpoints for clinical trials in primary sclerosing cholangitis. *Hepatology*. 2018;68:1174-1188.
140. Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology*. 2010;52:730-742.
141. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: The influence of age and sex. *Hepatology*. 2009;49:2001-2009.
142. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a french population-based study. *Hepatology*. 2002;36:451-455.
143. Padda MS, Sanchez M, Akhtar AJ, Boyer JL. Drug-induced cholestasis. *Hepatology*. 2011;53:1377-1387.
144. Sundaram V, Björnsson E. Drug-induced cholestasis. *Hepatol Commun*. 2017;1:726-735.
145. U.S. National Institute of Health (NIH). Liver tox: Clinical and researh information on drug-induced liver injury - acute hepatitis. https://livertox.nih.gov/Phenotypes_acutehepatitis.html. Accessed August 1, 2019.
146. Vroon DH, Israili Z. Alkaline phosphatase and gamma glutamyltransferase. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*, 3rd ed., Chapter 100. Boston, MA: Butterworths; 1990.
147. Ennulat D, Walker D, Clemo F, et al. Effects of hepatic drug-metabolizing enzyme induction on clinical pathology parameters in animals and man. *Toxicol Pathol*. 2010;38:810-828.
148. Bonkovsky HL, Kleiner DE, Gu J, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. *Hepatology*. 2017;65:1267-1277.
149. Kleiner DE. The pathology of drug-induced liver injury. *Semin Liver Dis*. 2009;29:364-372.
150. Moradpour D, Altorfer J, Flury R, et al. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. *Hepatology*. 1994;20:1437-1441.
151. Black M, Billing BH. Hepatic bilirubin udp-glucuronyl transferase activity in liver disease and gilbert's syndrome. *N Engl J Med*. 1969;280:1266-1271.
152. Owens D, Evans J. Population studies on gilbert's syndrome. *J Med Genet*. 1975;12:152-156.
153. Claridge LC, Armstrong MJ, Booth C, Gill PS. Gilbert's syndrome. *BMJ*. 2011;342:d2293.
154. Wolkoff AW, Berk PD. Chapter 5 bilirubin metabolism and jaundice. In: Schiff ER, Maddrey WC, Reddy KG, eds. *Schiff's Diseases of the Liver*, 12th ed. 2017. https://doi.org/10.1002/9781119251316.ch5
155. Fretzayas A, Moustaki M, Liapi O, Karpathios T. Gilbert syndrome. *Eur J Pediatr*. 2012;171:11-15.
156. Kathemann S, Lainka E, Baba HA, Hoyer PF, Gerner P. Gilbert's syndrome–a frequent cause of unconjugated hyperbilirubinemia in children after orthotopic liver transplantation. *Pediatr Transplant*. 2012;16:201-204.
157. Harb R, Thomas DW. Conjugated hyperbilirubinemia: Screening and treatment in older infants and children. *Pediatr Rev*. 2007;28:83-91.
158. Strassburg CP. Pharmacogenetics of gilbert's syndrome. *Pharmacogenomics*. 2008;9:703-715.
159. Botros M, Sikaris KA. The de ritis ratio: The test of time. *Clin Biochem Rev*. 2013;34:117-130.
160. Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH. Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. *J Clin Gastroenterol*. 1995;20:215-219.
161. Strople J, Lovell G, Heubi J. Prevalence of subclinical vitamin k deficiency in cholestatic liver disease. *J Pediatr Gastroenterol Nutr*. 2009;49:78-84.
162. Nassal M. Hbv cccdna: viral persistence reservoir and key obstacle for a cure of chronic hepatitis b. *Gut*. 2015;64:1972-1984.
163. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560-1599.
164. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with hepatitis b virus (hbv) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer*. 2004;90:1306-1311.
165. Reuben A. Hy's law. *Hepatology*. 2004;39:574-578.
166. Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf*. 2006;15:241-243.
167. U.S. Food & Drug Administration (FDA).Guidance for industry drug-induced liver injury: Premarketing clinical evaluation; 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liverinjury-premarketing-clinical-evaluation. Accessed July 1, 2019.
168. Van der Woerd WL, Houwen RH, Van de Graaf SF. Current and future therapies for inherited cholestatic liver diseases. *World J Gastroenterol*. 2017;23:763-775.
169. Chen HL, Wu SH, Hsu SH, Liou BY, Chen HL, Chang MH. Jaundice revisited: recent advances in the diagnosis and treatment of inherited cholestatic liver diseases. *J Biomed Sci*. 2018;25:75.
170. Bull LN, Thompson RJ. Progressive familial intrahepatic cholestasis. *Clin Liver Dis*. 2018;22:657-669.

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