CLINICAL INVESTIGATION

Approaches to the design of clinical trials for primary sclerosing cholangitis

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Clinical trial design is one of the most important aspects of advancing therapeutic interventions in the management of chronic liver diseases. Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of uncertain etiology and pathogenesis. The natural history of PSC is often assessed through a variety of clinical and histological end points. However, none of the therapeutic options examined in clinical trials for PSC to date has demonstrated benefit in halting or slowing disease progression. Furthermore, the emerging recognition of several subtypes in PSC, coupled with limitations in histological and cholangiographic staging, makes subject stratification and trial design challenging. This article will review approaches that have been used for designing clinical trials for assessing potential therapies for PSC as well as provide recommendations on future clinical trials design and explore the potential use of novel surrogate end points that may improve patient selection and treatment efficacy assessment.

Keywords: cholangiocarcinoma • clinical trials • end points • entry criteria • liver biopsy • overlap syndrome • primary sclerosing cholangitis • prognosis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, characterized by progressive inflammation, fibrosis and destruction of intrahepatic and extrahepatic bile ducts leading to end-stage liver disease [1–4]. PSC is an uncommon yet important chronic liver disease. A meta-analysis evaluating eight epidemiological studies has reported a pooled incidence rate of PSC at 0.77 (range: 0.45–1.09) per 100,000 person years. The incidence of PSC appears to be similar in North American and European countries and, more importantly, is increasing over time. Data on the incidence of PSC in developing countries are less well known [5]. PSC is most often diagnosed in the fifth decade of life in conjunction with a history of inflammatory bowel disease (IBD). The prevalence of IBD in PSC varies between 60 and 80% among North American and European populations [6]. Nearly 80% of patients with PSC and IBD have chronic ulcerative colitis, while a smaller number have Crohn's ileocolitis or indeterminate colitis. Patients with a combined diagnosis of PSC and IBD are also at an increased cumulative risk of colorectal neoplasia compared with patients with IBD alone [7].

Nearly 50% of patients with PSC are asymptomatic at diagnosis, yet some individuals present with fatigue, pruritus, jaundice or fever associated with biliary obstruction. Elevated serum alkaline phosphatase is the predominant biochemical finding in patients with PSC. However, serum levels may fluctuate in and out of the normal range during earlier stages of the disease. Serum aminotransferase values are moderately elevated while total serum bilirubin and albumin levels are usually within normal limits in the absence of jaundice [8]. Serum antinuclear, anti-smooth muscle, and anticardiolipin antibodies are also found, to variable degrees, in patients with PSC. To date, the prognostic relevance of carrying

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particular serum autoantibodies remains unknown [9]. Patients may also have elevated serum IgG4 levels, which may reflect a unique subtype of PSC (see section titled 'Clinical subtypes of PSC').

The gold standard for diagnosing PSC is cholangiography, which demonstrates multiple strictures with intervening areas of saccular dilatation involving the intra- and/or extra-hepatic bile ducts. In a study of 100 patients with PSC, strictures involving extra- and intra-hepatic ducts occurred in 87 patients, intrahepatic ducts alone among 11 patients, and extrahepatic ducts alone in two patients [3]. Conversely, some patients with early-stage PSC only have shallow ulcerations of the bile ducts in the absence of overt structuring [3]. The most frequently used modality to identify PSC is magnetic resonance cholangiopancreatography (MRCP), which is recognized as accurate and cost-effective [10]. For symptomatic patients at diagnosis, the diagnosis is established most often with endoscopic retrograde cholangiopancreatography (ERCP), where therapeutic interventions are performed to relieve biliary obstruction. While cholangiography is required for diagnosis, clinical trials to date have not used the extent or distribution of cholangiographic findings for stratification or end point assessment.

In clinical practice, a liver biopsy is not required to make the diagnosis of PSC when typical findings on cholangiography are observed. In general, histologic features of PSC have little specificity, yet destruction of the bile ducts with varying degrees of hepatic fibrosis is commonly observed as the disease advances. Liver biopsy is mandatory in patients with unexplained cholestatic serum liver enzyme profiles to rule out the possibility of small duct PSC or, in rare cases, overlap syndrome with autoimmune hepatitis (AIH). Histological findings do allow for staging of PSC, which has been used in stratifying patients for clinical trials.

The most feared complication of PSC is cholangiocarcinoma (CCA). Patients with PSC have a 10–20% lifetime risk of developing CCA with the highest risk being within the first year of PSC diagnosis. Thereafter, the annual incidence rate for CCA in PSC is between 0.5 and 1.5% [11]. Unfortunately, the diagnosis of CCA is very difficult to obtain and requires the use of multiple serologic imaging and endoscopic tests over time. Furthermore, there are no criteria for risk stratification to identify a high-risk group for enhanced surveillance within the PSC population. Thus, all patients are recommended to undergo annual surveillance for CCA with serum carbohydrate 19–9 (CA 19–9) antigen levels and MRCP or ultrasonography [12]. From a clinical trial perspective, the development of CCA is often considered an important end point. However, the development of CCA also results in reduced study power, given that it is a competing risk for other trial end points including survival or need for liver transplantation.

The natural history of PSC is defined by progression to biliary cirrhosis and end-stage liver disease over a median time period of 10–15 years from diagnosis [8,13]. Furthermore, the presence of abnormal serum liver biochemistries could identify patients at earlier stages where survival is prolonged. It is worth noting, that asymptomatic patients at presentation can also progress to end-stage liver disease [14,15].

At the present time, there has been no effective treatment identified to halt or slow the progression of PSC. A variety of anti-inflammatory and immunosuppressive agents have been tested with limited success and no evidence for survival benefit [16]. A systemic review described eight randomized clinical trials looking at the efficacy of bile acids (ursodeoxycholic acid [UDCA]) at various doses for the management of PSC. All trials had a high risk of bias and showed no improvement in clinical outcomes. However, improvement of biochemical parameters was present and UDCA was well tolerated except at the highest doses (28–30 mg/kg/day) where it increased adverse events. Hence, evidence regarding the use of UDCA for PSC is lacking and recommendation for (due to the biochemical improvement) or against (due to adverse events at high doses) the use of UDCA in PSC is therefore uncertain [16]. A recent Cochrane systemic review identified two randomized clinical trials looking at the usage of glucocorticoids for the management of PSC. The first trial, using biliary lavage in combination with hydrocortisone versus saline (control), was terminated due to increased occurrence of adverse effects. The second trial, looking at budesonide versus prednisone, did not conclude efficacy and, therefore, evidence for a beneficial effect on clinical outcomes of using glucocorticoid therapy is lacking. The weaknesses of the trials include having a small study subject population, with the first trial having 17 patients and the second 18 patients. In addition, the second trial did not compare glucocorticoid treatment to placebo [17]. Finally, a review of a single randomized clinical trial looking at the usage of D-pencillamine for PSC has concluded that it does not affect outcomes and, therefore, should not be used. Although a good number of patients (n = 70) were enrolled to the study, no improvement in clinical outcomes was significant and adverse events were increased. The reason for these results could be in part attributed to the poor methodological design of the study, which may have

altered the significance of the results [18].

In turn, PSC remains the fourth most common indication for liver transplantation in adults within the USA. Following liver transplantation, patient and graft survival in PSC are among the highest when compared with more common indications for transplant, with 5-year survival rates >80% [19]. Notably, PSC may recur in up to 30% of patients following liver transplantation [20,21].

Clinical subtypes of PSC

PSC–IBD

PSC is commonly associated with underlying IBD, with prevalence rates estimated at 60–80% [5,22]. The majority of patients have ulcerative colitis (80%), while Crohn's ileocolitis (10%) and indeterminate colitis (10%) comprise the remaining cases [23]. The diagnosis of IBD may or may not predate the clinical presentation of PSC. Recent studies have suggested that PSC–IBD represents a distinct 'third' IBD subtype, with several distinguishing features including backwash ileitis, increased right-sided inflammation of the colon, rectal sparing and an increased risk of pouchitis following proctocolectomy [23–26]. A remarkable feature of the PSC–IBD subtype is the increased risk of developing colorectal cancer when compared with IBD patients without PSC [27–29]. A recent observational study has described the association between an increased risk of disease progression and a need for liver transplantation in subjects with clinically quiescent IBD, as opposed to patients with active IBD [30]. Confirmation of this observation would add knowledge about clinical activity of IBD as a prognostic factor.

PSC without IBD

The subset of patients having PSC without underlying IBD, has distinctive features when compared with the general population of PSC patients. Unique characteristics include a lower male:female ratio and increased frequency of symptoms at presentation. It is worth noting that this subset of patients with isolated PSC may also have a better prognosis than patients with PSC and underlying IBD [31].

Small-duct PSC

Small-duct PSC is a subtype used to describe patients lacking cholangiographic abnormalities associated with PSC but showing typical biochemical and histological features. Isolated small-duct involvement is estimated to represent 5–10% of the total PSC population and is associated with higher survival rates when compared with subjects with diffuse changes in PSC [32,33]. In three different cohorts of patients with small-duct PSC, no individual patient was observed with subsequent CCA; and the majority that survived did not require liver transplantation [32–34]. In total, <25% of patients progress to large-duct PSC [35].

IgG4 sclerosing cholangitis

IgG4 sclerosing cholangitis presents with clinical and radiographic features similar to PSC and is commonly associated with autoimmune pancreatitis [36]. Autoimmune pancreatitis, a term introduced by Yoshida *et al.* in 1995, is a subtype of chronic pancreatitis that demonstrates an excellent response to steroid therapy [37,38]. Furthermore, patients with autoimmune pancreatitis may also have biliary tract involvement (termed autoimmune sclerosing cholangitis) that can resemble the cholangiographic changes seen in PSC. The diagnosis of autoimmune pancreatitis can be confirmed by using the five cardinal features: histology, imaging, serology, other organ involvement, and response to steroid therapy. These can be summarized in the mnemonic 'HISORt' [39]. This is supported by the presence of plasma-cell infiltrates in the pancreas and extrapancreatic tissue that immunostain for IgG4. It is important to note that IgG4 sclerosing cholangitis shows a dramatic response to steroid therapy and relapses occur when steroid therapy is withdrawn [40].

A recent study suggested that some individuals with PSC–IBD will also have elevated serum IgG4 levels and that an increased risk for progression to liver transplantation or death may be seen in these patients, compared with other PSC patients with normal serum IgG4 levels [41]. When identifying subjects with IgG4 sclerosing cholangitis, the use of specific criteria is helpful, including an elevated IgG4 level, exclusion of IBD, exclusion of malignancy by bile duct biopsy, typical intraductal sonographic findings and utilization of liver biopsy [42].

AIH–PSC overlap syndrome

A small number of patients will present or develop features consistent with an overlap syndrome between AIH and PSC. Typically, the presence of clinical, biochemical and histological features of both AIH and PSC are recognized in making this diagnosis. Patients with AIH–PSC overlap syndrome may present at an earlier age and have higher serum AST, ALT and IgG levels when compared with subjects with typical PSC [43]. Anecdotal evidence to date suggests that individuals with AIH–PSC overlap syndrome may benefit from immunosuppressive therapy with or without UDCA [43].

Design of clinical trials for PSC

The design and execution of clinical trials involving patients with PSC is affected by several challenges. PSC is a relatively uncommon disease and therefore attaining a sufficient sample size often requires substantial effort. In addition, the varying disease severity and differing rates of progression among individual patients makes unifying results and reaching meaningful conclusions difficult in pilot investigations. Despite the use of randomization, the small number of patients typically enrolled in Phase II studies does not always guarantee that prognostic factors (known and unknown) have been adequately balanced. Moreover, due to the presence of several subtypes of PSC with distinct clinical features, complications and response to therapy, the generalization of results may be difficult [44]. Ultimately, PSC is a chronic disease that requires prolonged periods of follow-up to detect the effects of therapy and/or clinical outcomes influenced by tested therapies. Thus, it is imperative to identify and incorporate surrogate markers in Phase II studies that identify efficacy for novel agents being tested and more accurately predict the development of medium-term clinical outcomes in subsequent Phase III studies.

Phase II studies

For short-term studies (Phase I and IIa) designed mainly to assess the tolerability of new drugs and initial evidence of efficacy, an examination of improvement in serum liver biochemistries and prognostic model indices, such as the Mayo PSC risk score, have been and will continue to be used as primary end points [45–47]. Novel approaches including changes in disease distribution by MRCP and noninvasive measures of hepatic fibrosis, including serum markers and liver stiffness (by ultrasound or MR elastography) should also be included as secondary end points.

A current issue of controversy with Phase II studies relates to the role of randomization. Many open-label, Phase II studies are designed as single-arm trials in other disciplines (e.g., oncology), as the safety and initial efficacy of many agents studied are unknown. On the other hand, when a comparator treatment has some effect on the disease (e.g., UDCA in the example of primary biliary cirrhosis [48,49]), the use of randomization of the new treatment versus the matched placebo (with background use of the established treatment) is a reasonable approach. It would appear that the existence of synergy between UDCA and a novel agent could apply, and thus combination therapy should also be examined whenever possible. However, when no proven benefit of the studied therapy has been established (e.g., UDCA in the example of PSC [16,45,50,51]), then randomized placebo-controlled trials are warranted and this applies for most therapies investigated in patients with PSC. Responders to UDCA showing biochemical improvement should not be excluded from novel trials if they show interest in the suggested therapy and are willing to comply [16,45,51]. Sufficient time should be provided between discontinuation of UDCA therapy and starting the new regimen. PSC patients with a biochemical response to UDCA therapy who are reluctant to UDCA removal, may be enrolled in placebo-controlled studies using a combination therapy where UDCA is utilized as part of the regimen.

Phase III studies

The primary objective of Phase III clinical trials in PSC is to demonstrate a survival benefit in association with reducing the development of liver-related complications, including hepatobiliary neoplasia. As previously discussed, a significant level of effort and resources are needed to undertake and maintain Phase III studies, given the length of follow-up they have required. In turn, there is increasing hesitation with moving from Phase II–III as a number of positive results in smaller studies have not been reproduced in larger populations. Confirming the validity of novel end points for assessing treatment effect and incorporating these markers in earlier phase studies should improve the likelihood of seeing positive results in larger trials.

Entry criteria

A detailed description of the diagnosis of PSC in clinical practice is beyond the scope of this report; however, the interested reader is referred to the recent American Association for the Study of Liver Diseases practice guidelines published on PSC [6].

Serum liver biochemistry values

Patients with PSC usually present with biochemical test values reflecting the presence of cholestasis. Elevated serum alkaline phosphatase levels are the most common biochemical abnormality at presentation [22,52]. Elevation of serum aminotransferase (AST and ALT) levels up to two- to three-times the upper limit of normal is also common. Conversely, some patients have normal serum alkaline phosphatase and serum aminotransferase levels at presentation. In turn, these patients do not usually meet entry criteria for clinical trials. Unlike other biochemical markers, total serum bilirubin levels are normal at diagnosis in the great majority of PSC patients [6,53]. For entry criteria within clinical trials, it is best to include patients with persistently elevated serum alkaline phosphatase

levels at least twice the upper limit of normal. Serum total bilirubin levels should also be between normal and twice the upper limit of normal in the absence of a clinically significant extrahepatic biliary stricture.

Cholangiography

Patients with typical bile duct changes associated with PSC on MRCP or ERCP in the setting of a cholestatic serum liver-enzyme profile should be considered for inclusion into clinical trials. Specific cholangiographic findings that characterize PSC are multifocal short, annular strictures, alternating with normal or slightly dilated segments, producing a 'beaded' pattern. Patients with either intrahepatic or diffuse (intrahepatic or extrahepatic) biliary strictures should be considered eligible. The presence of long confluent extrahepatic strictures (especially in the hilum) may indicate the presence of CCA that requires confirmation or exclusion prior to study entry if clinically indicated. The presence of a periductal mass on MRI, for example, is highly suspicious for CCA [54,55]. Subjects with a history of dominant benign strictures requiring frequent endoscopic intervention will need to be considered for enrollment on a case-by-case basis [56]. Patients with clinical, biochemical and histological features of PSC and normal cholangiography should be classified as small-duct PSC [57]. Given the more favorable prognosis on this subtype, it is probably best to exclude these patients from novel clinical trials or, at a minimum, subject them to stratified randomization so their participation is balanced when multiple treatment arms are used.

Liver histology

From a clinical perspective, the performance of a liver biopsy is not required for a diagnosis of PSC in the presence of compatible features on cholangiography [44]. However, the acquisition of liver histology is quite useful for staging individual patients and to facilitate randomization with respect to the presence of advanced hepatic fibrosis (i.e., stages 3–4; Table 1). In rare cases, a liver biopsy may need to be performed to rule out the existence of AIH–PSC overlap syndrome so that these individuals receive specific therapy outside of clinical trials [43]. Furthermore, liver histology may also be used as a clinical end point showing histological progression of PSC in longer term studies. It should be noted that sampling variability on liver biopsy in PSC is quite broad and that the potential exists for understaging hepatic fibrosis on an individual basis [58]. When clinical trials are developed for assessing improvement in symptoms or other nonhistological end points, it is less imperative to perform a liver biopsy prior to study entry.

Table 1. Histological findings in various stages of primary sclerosing cholangitis.

Primary sclerosing cholangitis stages	Histological finding
Stage 1	Degeneration of epithelial cells in the bile ducts and inflammation of the portal triads with mononuclear infiltration and piecemeal necrosis
Stage 2	Fibrosis expanding into the parenchyma with dilation of the portal triads
Stage 3	Bridging fibrosis
Stage 4	Cirrhosis

Exclusion criteria

PSC is a rare condition and thus the design of clinical trials for this population must be specific yet inclusive. However, a number of criteria do require identification to preserve the internal validity of clinical trials. Patients with symptomatic, untreated biliary strictures and/or evidence of bacterial cholangitis are typically excluded as these findings may confound the assessment of serum biochemical changes for either active or placebo-treated arms. Subjects with CCA or decompensated cirrhosis have more disease-related complications and reduced survival than less-complicated PSC patients and, thus, require exclusion from therapeutic trials [59]. Similarly, patients awaiting liver transplantation are typically excluded as the receipt of liver transplantation will cause patients to be censored from reaching study end points.

Many patients with inflammatory bowel disease receive immunosuppressive or biologic therapies that could influence the therapeutic response observed in clinical trial settings. Thus, pilot studies assessing new therapeutic options may require the exclusion of IBD patients receiving these treatments. However, there has been no evidence to show that these IBD-specific therapies have a significant effect on serum liver biochemistries or disease trajectory in PSC. Future studies examining this population should be developed to allow these patients access to novel therapies for PSC.

Subject stratification

The assessment of variables that may be affected by disease progression or confounding factors, may lead to bias within study results. Therefore, it is essential that patients are stratified at baseline according to these variables. Although randomization may help minimize bias, the stratification of subjects will ensure that known factors that could dynamically affect outcomes are distributed evenly between treatment arms. Stratification is more useful in trials with

limited patient numbers, whereas trials involving larger patient populations may be more likely to use simple randomization.

Natural-history models may also provide direction in terms of important factors that should be considered for stratification in clinical trials. Several models utilizing Cox-proportional hazards regression analysis have been developed to predict survival in patients with PSC. One of the most commonly used models is the Mayo PSC risk score [8], which was later refined to exclude histology and, therefore, eliminate the need for liver biopsy in predicting survival [60,61]. The Mayo PSC risk score involves a simple mathematical formula constituting five variables (age, total bilirubin, serum albumin, AST and variceal bleeding) that assess survival in PSC patients. In previous studies, the Mayo PSC risk score has helped to predict the estimated survival of patients in relation to treatment response in clinical trials [62].

The selection of individual variables (Box 1) used for patient stratification may also depend on the end point. For shorter studies assessing the improvement in symptoms, the goal of stratification according to biochemical parameters or baseline symptom status may be important. When trials are longer and aimed at assessing disease progression, then stratification according to disease stage is of value. Clinical trials aiming at testing novel therapeutic options may need stratification of PSC patients according to the clinical subtype of PSC as well. For example, serum IgG4 levels have not been recognized as a prognostic or stratification variable in the past but could be used to stratify patients and improve the balance in randomization.

When conducting clinical trials to evaluate novel therapies, stratification in terms of disease severity should be avoided. Such stratification could lead to patients with early-stage disease receiving the drug and patients with late-stage disease receiving the placebo, or *vice versa*. As patients with late-stage PSC are likely to suffer worse outcomes, this could bias the results of the trial leading to the medication being rendered efficacious when in reality it was merely used in a group with better prognosis (early-stage patients). This can be avoided by staging patients at entry and randomizing patients from each group (early/late stage) into the therapy or placebo arm to create a balanced study population.

Box 1. Factors involved in subject stratification.

Biochemical features
- Mayo risk score (albumin, AST, total bilirubin)
- Normalization of alkaline phosphatase level†

Histology
- Stage of PSC at entry†
- Cirrhosis or fibrosis on liver biopsy†

Subtype of PSC
- Elevated IgG
- Small duct PSC†
- IBD positive/negative†
- AIH overlap†

Presence of disease complications
- Portal hypertension
- Esophageal varices

Radiologic features
- Degree of fibrosis on magnetic resonance elastography

†Denotes factors of most importance.

AIH: Autoimmune hepatitis; IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis.

Duration of trials

The recommended duration of PSC trials depends on the end points assessed in a specific trial. Study duration must ensure that a measurable change in selected end points can develop in a prespecified proportion of subjects under study. In an earlier trial of UDCA therapy for PSC patients, a biochemical response was achieved after a median treatment period of 3 years (range: 3–36 months) [16]. Hence, based on the known fluctuations of serum biochemistries a minimum duration of 3 months is suggested for examining treatment end points, such as biochemical values or change in symptom severity. Conversely, a minimum trial duration of 3–5 years is suggested for examining clinical and/or histological outcomes, this is based on our assessment of the natural history and histologic progression of PSC. It is worth noting that the value of serial liver biopsies in assessing treatment efficacy is limited by the increased frequency of sampling error in PSC [63].

Power estimates

Clinical end points consist of primary and secondary outcomes that are used to measure the efficacy of an intervention. Primary end points are used to denote events that form an important aspect of the disease process and, therefore, altering the frequency or time to occurrence of such end points is a major aim of the therapeutic intervention. On the other hand, when the effects on primary end points are similar between two regimens, secondary end points can aid in choosing the regimen with the better overall effect. In some clinical trials, the inclusion of several primary end points may be needed and, depending on the trial design, the drug is deemed efficacious when it alters one or all of such end points. Conversely, this can complicate the statistical analyses, produce

erroneous conclusions and lead to flawed decisions. Usage of multiple primary end points can affect the probability of achieving statistical significance, which may hinder the ability to establish the therapy as efficacious. This can be overcome by utilizing statistical methods to help improve the study power or selecting a single primary end point (e.g., overall survival) to establish efficacy [64].

Power estimates are crucial to determine the number of patients needed for enrollment in a clinical trial. This depends on the clinical end points being used and the selected study population (e.g., primary biliary cirrhosis, PSC and overlap syndrome). Due to the relative rarity of primary liver disease in the general population, it is often a challenge to enroll a sufficient number of patients in clinical trials. In such situations, well-powered single-arm trials may be favored initially over underpowered, randomized placebo-controlled trials for the investigation of new therapies. Once a positive trend for efficacy is established then patients may be more receptive to enrollment and randomized placebo-controlled trials that can achieve statistical significance may become plausible.

End points of clinical trials

Clinical end points are essential components for assessing the outcomes of patients with PSC. End points may either be assessed directly (i.e., death, liver transplant) or indirectly through the use of surrogate end points (e.g., development of esophageal varices to assess portal hypertension). Surrogate end points are indirect biomarkers that are intended to substitute for direct clinical end points such as death or liver transplantation. This is often utilized when the number of events is small and hence hinders the trial from approaching statistical significance. Surrogate end points can be classified as intrinsic or extrinsic and then further subdivided according to function as markers used for diagnosis, determining therapeutic response or monitoring the progression of disease. The usefulness of surrogate end points depends on understanding the pathophysiology of the disease and the exact mechanism in which the intervention acts. In cholestatic diseases, such as PSC, the pathophysiology remains obscure and hence usage of 'soft' surrogate end points alone (e.g., esophageal varices) can be problematic. Confounding factors can often affect surrogate end points and therefore their validity of reflecting 'hard' end points, such as death or time to liver transplantation, is debatable [65].

Serum biochemical markers

Based on the observation that serum alkaline phosphatase elevation is the most common biochemical abnormality in PSC [22,52], its use as a study end point in clinical trials is now being recognized as essential. Conversely, limitations to the use of serum alkaline phosphatase as an end point, include normal values in some patients with PSC and spontaneous fluctuations in its levels during disease progression. Serum aminotransferases are also elevated in the majority of patients with PSC and may also be utilized as end points to assess biochemical response in conjunction with alkaline phosphatase. Serum total bilirubin is within normal limits in approximately 70% of patients at diagnosis. However, a reduction in slightly elevated serum total bilirubin levels may be of value in patients with advanced PSC who are eligible for clinical trials.

Death/liver transplant

Historically, the median survival free of liver-transplantation in patients with PSC is approximately 10–12 years, with further reductions in longevity if features of advanced disease (i.e., ascites) are present at the time of diagnosis. For Phase II study designs, these end points cannot be examined directly given the overall purpose of these trials and their short duration. However, overall survival and liver transplantation are required for subsequent Phase III studies based on promising data from Phase II trials.

Liver histology

When assessing end points such as cirrhosis, the presence of typical findings on a histological sample from a liver biopsy is required. As previously mentioned, the strict reliance on liver histology to determine whether fibrosis progression has occurred is not precise or reproducible enough for use as a reliable end point alone. Typically, the inclusion of histology as one element of a composite end point is performed and is currently recommended. Again, the need for liver histology is clearer in Phase III clinical trials settings, although histology in some Phase II setting could be justified, depending on the mechanism of action being tested.

CCA

Patients with PSC are at increased risk of CCA. The annual incidence of CCA in the setting of PSC is estimated at 1.5% with a cumulative lifetime risk of 10–15%. Potential risk factors described in the literature for CCA include long-standing inflammatory bowel disease, prior variceal bleeding and colorectal dysplasia or carcinoma [66,67].

Confirming the development of CCA within a clinical trial may be difficult as multiple techniques

including cytology, bile-duct biopsy, serum tumor markers (CEA and CA 19–9) and imaging (CT scan and MRI) are often required. However, patients with a clinical suspicion of CCA or those who require follow-up testing to confirm or refute the diagnosis should probably not be enrolled in clinical trials. Unfortunately, there is no highly sensitive method for screening patients with PSC to exclude CCA.

Portal hypertension

Portal hypertension is a common complication and constitutes part of the natural history for patients with cirrhosis related to PSC. It may be assessed indirectly through the identification of esophageal varices or directly by measuring the hepatic venous pressure gradient. Note that hepatic venous pressure gradient results, in patients with PSC, may underestimate the degree of portal hypertension that exists, given the pathogenesis of hepatic fibrosis in PSC [68]. In clinical trial settings, the inclusion of overt complications related to portal hypertension as study end points is recommended for longer term studies (>2 years), as effective therapy could reduce the probability of their occurrence. For shorter term studies, the inclusion of portal hypertensive-related end points is not strongly recommended.

Symptoms

Symptoms associated with PSC, including fatigue and pruritus, are relevant clinical and study end points. Quantitative methods for assessing these symptoms will help to improve their precision and to minimize reporting bias by subjects and observers. Furthermore, these symptom-based studies will require a matched placebo group to discern the actual effects of active treatment. For example, the 5-D itch scale for measuring pruritus was established and validated as a multidimensional measure of itching severity [69]. Similar validated indices for other symptoms, in addition to overall health-related quality of life, should be incorporated in clinical trials for patients with PSC.

Novel end points

One key to improving the efficacy assessment for treatments in Phase II studies is to develop and incorporate surrogate end points that have biological and prognostic relevance to hard end points used in Phase III trials [70–74]. Imaging has not been widely utilized as an end point for clinical trials to date. This can be attributed to several factors, including the limited availability of imaging modalities at different institutions, provider-related bias in interpreting imaging results and center-related variability (imposed by variability of equipment and techniques). Such limitations make imaging a less reliable end point and marker in clinical trials. On the other hand, serial cholangiographic examinations among patients with PSC have become more widespread in clinical practice based on advances in MRCP technology, which could mean that such modalities will soon become reliable for following the disease progression and possibly evaluating drug efficacy. In turn, the ability to obtain 3D images with improved spatial visualization of intrahepatic bile ducts makes this approach appealing for use in clinical trials. To date, initial studies have not confirmed a role for the spatial distribution of biliary strictures assessed by ERCP as a prognostic factor [75], but perhaps future studies examining 3D MRCP will demonstrate that it could be a valid surrogate end point for use in clinical trials.

Elastography (ultrasound or MR) is a novel technique that can be utilized to measure liver stiffness in a noninvasive manner. Notably, this can also be done in conjunction with an MRCP (when MR elastography is available). To date, studies have shown that elastography is a reliable and valid noninvasive method for the measurement of liver fibrosis and assessing progression of liver disease [70,73,74,76,77]. From a clinical trial perspective, the potential advantage of elastography is its ability to demonstrate improvements in liver elasticity at specific timepoints within a trial and how often this occurs in patients achieving a biochemical response to novel therapies. Furthermore, it can be used in place of, or with, liver biopsy to confirm stage of disease prior to study entry.

Serum fibrosis markers will also be helpful noninvasive tools to assess the degree of hepatic fibrosis in clinical trials for PSC. These markers are classified as direct (representing components of extracellular matrix) or indirect (reflecting hepatic inflammation and function) [78]. The most commonly used indices for detection of hepatic fibrosis are the FibroTest, APR and enhanced liver fibrosis panels [79]. The practical advantages of serum fibrosis markers include their noninvasiveness, potential for widespread availability and reproducibility when serial examinations are performed using the same laboratory. However, the majority of studies to date have involved patients with chronic HCV infection, yet satisfactory diagnostic performance for detecting cirrhosis (stage F4) has been identified for direct and indirect marker panels. The detection of clinically significant hepatic fibrosis (stages F2–F4) is not as robust when compared with cirrhosis [78]. Recently, the prognostic value of serum fibrosis markers have been demonstrated [80]. Although their role in PSC patients has not been investigated thoroughly, future trials involving noninvasive serum fibrosis (as well as proteomic) markers will help

advance the assessment of treatment response in PSC.

Prognostic/natural history models

It is worth noting that the Mayo PSC risk score is superior to the Child–Turcotte–Pugh score in providing valid survival information, especially in patients with early-stage disease from PSC. Conversely, these models are insensitive to small changes that may be of importance in ascertaining the preliminary efficacy of novel agents within clinical trials. Therefore, we would encourage use of the Mayo PSC risk score as a secondary end point in clinical trials.

Evaluation of epidemiologic studies

Epidemiologic studies in patients with PSC are needed to enhance the understanding of the causes, prevention and treatment of the disease process. This understanding will improve the construction of future clinical trials aimed at establishing effective novel therapies. It is worth noting that to conduct a successful epidemiologic trial, several criteria should be taken into account. The 'epidemiologic appraisal instrument' developed by Genaidy *et al.* may help define such criteria; this instrument focuses on several components, including reporting, subject/record selection, measurement quality, data analysis and generalization of results [81]. This tool can be utilized to design new epidemiologic studies or evaluate existing studies. The quality of epidemiologic studies can also be improved by studying inception cohorts (a cohort of patients identified at the earliest point in the course of the disease), assuring an adequate length of follow-up and adjusting for specific variables as required by the study design.

Future perspective

With the exception of liver transplantation, no current therapy has been identified as effective for slowing the progression of PSC. Progression is often measured by the development of several clinical end points, such as cirrhosis, esophageal varices, CCA or liver-related mortality. If novel end points can be identified as valid predictors of eventual disease progression, then a more accurate assessment may be possible for therapeutic interventions applied to this population in the future. The incorporation of noninvasive biochemical and imaging techniques in assessing liver injury and

Executive summary

- Primary sclerosing cholangitis (PSC) is a rare disease with many phenotypic subtypes and causative etiologies.
- Clinical trials involving patients with PSC are affected by many challenges.
- Randomization in Phase II studies is a current issue of controversy and a significant amount of effort and resources are needed for Phase III studies.
- Biochemical responders to ursodeoxycholic acid should not be excluded from trials if they show interest.
- Novel end points for assessing treatment affect will improve the likelihood of seeing positive results in larger trials.
- Including several primary end points may be needed but can complicate the statistical analysis and produce erroneous conclusions.
- Once a positive trend for efficacy is established then patients may be more receptive to enrollment and randomized placebo-controlled trials.
- Patients with cholangiocarcinoma or decompensated cirrhosis and patients awaiting liver transplantation should be excluded.
- Natural history models provide direction in terms of important factors that should be considered for stratification.
- Shorter studies (minimum of 3 months) to assess improvement in symptoms: stratify according to biochemical parameters or baseline symptom status.
- Longer studies (minimum of 3–5 years) to assess disease progression: stratify according to disease stage.
- When conducting clinical trials to evaluate novel therapies, stratification in terms of disease severity should be avoided.
- Confounding factors can often affect how surrogate end points reflect definite end points such as death or time to liver transplantation.
- Serum ALP, serum ALT and serum total bilirubin can be utilized as end points to assess the biochemical response to therapy.
- The strict reliance on liver histology to determine whether fibrosis progression has occurred is not precise or reproducible.
- The inclusion of histology as one element of a composite end point is recommended.
- Patients with a clinical suspicion of cholangiocarcinoma should not be enrolled in clinical trials.
- Inclusion of complications related to portal hypertension as study end points is recommended for longer term studies (>2 years) but not short-term studies.
- Symptom-based studies will require a matched placebo group to identify the actual effects of active treatment.
- Novel imaging techniques and serum fibrosis markers will be helpful noninvasive tools to assess the degree of hepatic fibrosis in clinical trials for PSC.
- The quality of epidemiologic studies can be improved by studying inception cohorts, assuring adequate follow-up and adjusting for specific variables.
- Codifying specific diagnostic features of PSC will assist in enhancing patient selection for clinical trials.

treatment response in PSC will also be of significant importance in the future. Despite the problems associated with conducting randomized clinical trials in PSC patients (e.g., rarity of disease, population variability, absence of a surrogate marker that denotes disease progression and the prolonged period of follow-up required) the conduct of these studies remains feasible and many pilot studies are underway to identify novel therapeutic options. An example is a recent study by Martin *et al.*, which showed significant decline of ALP in PSC patients treated with docosahexaenoic acid [82]. The study was a 12-month, open-label, pilot trial with 23 PSC patients treated with docosahexaenoic acid 800-mg twice daily, which produced a significant improvement in mean ALP levels at 12-month follow-up compared with baseline.

Conclusion

PSC is a rare disease with many phenotypic subtypes and causative etiologies. Codifying specific diagnostic features of PSC will assist in enhancing patient selection for clinical trials. Use of appropriate study designs and inclusion of traditional and novel end points is expected to improve assessment of treatment efficacy of emerging therapies for PSC.

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