

## EDITORIAL

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“The ideal PSC patient to be entered into a clinical trial is one who is early in the course of their disease, but one who is likely to progress to cirrhosis. How can we identify such ‘progressors’?”

## Primary sclerosing cholangitis clinical trials: mission impossible ... for now

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This issue of *Clinical Investigation* has an excellent review of the inherent difficulties in performing clinical trials in patients with primary sclerosing cholangitis (PSC) [1]. The low number of suitable patients, need for a prolonged follow-up, and search for outcomes other than liver transplantation or death offer important challenges to investigators. These difficulties are seemingly insurmountable, but with more epidemiologic insights into the natural history of disease, these obstacles could be overcome.

PSC is a chronic inflammatory disease of the bile ducts and is strongly associated with inflammatory bowel disease. The median time from diagnosis to progression to cirrhosis is between 10 and 15 years. Many patients do not progress to cirrhosis; they can be followed expectantly for their lifetime, but do not ever require therapy. Alternatively, patients who have already developed cirrhosis are not likely to benefit from innovative treatment. The ideal PSC patient to be entered into a clinical trial is one who is early in the course of their disease, but one who is likely to progress to cirrhosis. How can we identify such ‘progressors’?

Histologic abnormality is a likely candidate for identifying patients. Histologic staging for PSC patients is listed in Table 1 in the article by Imam *et al.* [1]. By the time stage 3 or 4 disease is detected, it is not likely that an anti-inflammatory medication will help – these patients should be excluded from clinical trials. Patients with stage 1 disease may not be progressors and should be followed expectantly outside of a clinical trial. Stage 2 patients are ones who have progressed but are early on in the progression process. These patients may be the best candidates to be included in a clinical trial. Of course, limiting entry to only stage 2 patients limits the sample size dramatically and makes multicenter trials a necessity. Interestingly, liver biopsies are not routinely undertaken on PSC patients, may suffer from sampling error (leading to misclassification of staging), and are not included in the Mayo PSC Risk Score. While appealing, histologic staging may not be an ideal candidate to identify the appropriate patient for a clinical trial.

The Mayo PSC Risk Score uses five variables (age, bilirubin, albumin, AST and variceal bleeding) to estimate survival in PSC patients [1]. Perhaps, progressors can be identified by documenting a change in Mayo PSC Risk Score over a defined period of time. Such a strategy seems very reasonable in designing trials.

Are there certain populations of PSC patients that have a particularly high proportion that progress rapidly to cirrhosis? A better understanding of the

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natural history of the disease is needed in patients with:

- Autoimmune hepatitis–PSC overlap;
- IgG<sub>4</sub> positivity in PSC patients;
- Small-duct PSC (i.e., normal cholangiogram).

If progressors constitute a majority of patients in any of these populations, including them in clinical trials increases the chances of finding a treatment affect.

Identifying study outcomes, different from mortality and liver transplantation, could greatly shorten study duration, thereby improving feasibility and expense. Candidate surrogate markers, as mentioned in the Imam *et al.* article, include serum fibrosis markers, elastography and 3D cholangiography [1].

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With our current understanding of the clinical epidemiology of PSC, clinical trials have too many

important challenges. It seems clear that more epidemiologic data are necessary to better identify patients likely to benefit from innovative therapy. Patients with disease not likely to progress, or those who have progressed to later stage disease should be excluded from clinical trials. Finding the patient with early-stage disease who is likely to progress is the main challenge for all principal investigators. No one center will be able to enroll a sufficient number of patients, so a cooperative effort among investigators, patient advocate groups and pharmaceutical companies is needed. While the mission may seem impossible now, with focused epidemiology studies to identify the progressors, studies in PSC patients could lead to important therapeutic breakthroughs.

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#### Reference

- 1 Imam MH, Lindor KD, Talwaker JA. Approaches to the design of clinical trials for primary sclerosing cholangitis. *Clin. Invest.* 2(8), 769–780 (2012).