ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Predicting Outcomes of Primary Biliary Cholangitis Using the GLOBE Score

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G&H What is primary biliary cholangitis, and how prevalent is this disease?

MM Primary biliary cholangitis (PBC; until recently known as primary biliary cirrhosis) is a chronic liver disease in which the small and medium-sized bile ducts become damaged by the immune system. This leads to progressive cholestasis, which can eventually cause cirrhosis and even liver failure.

PBC affects women much more than men, at an approximately 12 to 1 ratio of women to men, and the incidence of this disease is increasing. One of the reasons for this increase is the fact that physicians are becoming better at diagnosing PBC earlier. There is a lot of variability in how common this disease is. Most estimates are between 12 and 20 per 100,000 individuals, with the highest estimates exceeding 60 per 100,000 individuals.

G&H What is the cause of this disease?

MM The cause is not entirely clear. The preponderance of evidence suggests that PBC is an autoimmune disease. This is because the disease is uniquely characterized by a loss of tolerance to the mitochondrial antigens, specifically the mitochondrial androgen pyruvate dehydrogenase. Because this loss of immune tolerance occurs in the earliest stages of the disease, it is suspected, although not proven, that the loss initiates the disease.

There is also some evidence that a virus may be pathogenic, but more data are needed to substantiate this theory.

G&H What is the usual prognosis of PBC? What are the most common consequences and complications of this disease?

MM Even at early stages, patients with PBC can have disabling symptoms of fatigue and itching. As the disease progresses and cirrhosis ensues, these patients develop the same complications as other patients with cirrhosis (ie, ascites, encephalopathy, variceal bleeding, liver cancer). There are also a myriad of associated conditions that cause additional morbidity, such as osteoporosis, Sicca syndrome, thyroid disorders, and arthritis.

G&H What are the most common treatment options for PBC?

MM Ursodeoxycholic acid, in a dose of 13 to 15 mg/kg, is the standard treatment for PBC in the United States and most of the world. Approximately 60% of patients with PBC will respond biochemically to ursodeoxycholic acid, and their survival is the same as that of the healthy control population. Therefore, approximately 40% of patients with PBC need some type of adjunctive therapy, although a group of researchers reported an even higher percentage at the recent meeting of the American Association for the Study of Liver Diseases. These are the patients for whom the GLOBE score project (so named for its data collection across the globe) was conducted—so that it would be possible to better determine which patients really belong to that nonresponder group, based on their prognosis and survival.

G&H What prognostic scores for PBC have been used in the past, and why was there a need to develop a new score?

MM There have been multiple studies published from individual centers that have examined biochemical predictors of survival after treatment with ursodeoxycholic acid, including the Mayo risk score, Rotterdam criteria, Paris 1 criteria, Paris 2 criteria, Toronto criteria, and Barcelona criteria. However, each score was developed and validated in a local population, and each obtained slightly different results.

In the GLOBE score, all of the raw data from each of the centers that previously reported their own score were combined, and then additional data from several other countries, including Italy, Japan, and the United States, were combined. The ultimate goal was to determine the best surrogate marker of disease progression in patients with PBC who were treated with ursodeoxycholic acid. This was a monumental international collaboration of long-term follow-up data of over 4000 patients with PBC who had been treated for at least 1 year with ursodeoxycholic acid and then followed for a median of 7.8 years.

G&H Specifically, what data comprise the GLOBE score?

MM The project was limited to variables that were easily and readily available, meaning patient demographics such as age and sex, as well as clinical and laboratory tests such as platelet count and levels of standard bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and albumin at 1 year of follow-up. This large population was divided into both a derivation and a validation cohort, and Cox proportional hazard regression modeling was applied, with the time to event analysis to determine which factors predicted death or transplant. Multiple multivariable models were created, and a final model was selected by the best fit using goodness-of-fit criteria.

G&H Has this score been validated?

MM No. However, almost every large historical PBC ursodeoxycholic acid study was included in this data analysis, so there is almost no other available data that could be used to validate it. The next level of validation would be to take several hundred patients with newly diagnosed PBC, treat them with ursodeoxycholic acid for a year, take a matched control population that is not treated, follow both the treated and untreated groups prospectively for a decade, and then monitor their survival and complications prospectively over another decade. However, that would be a nearly impossible study to conduct; no one would fund such a study. Therefore, I do not think that the GLOBE score sets itself up to be validated; it is as good of a prognostic score for PBC as realistically possible.

G&H Is this score ready for use right now?

MM Yes. Some pharmaceutical companies are already starting to calculate and use the score in the development phase of their clinical trials to determine which patients should be targeted.

In terms of clinical practice applications, I am not sure whether physicians are using the score yet in their daily practice, although a calculator is available online and soon there will be an app. In the future, the average gastroenterologist will likely be faced with multiple options for PBC therapy, so the onus will be on him or her to select the appropriate patients for the appropriate therapy and to make accurate prognoses. Patient selection will be important, and the GLOBE score will likely help in this matter.

G&H How can the score be used to select patients for clinical trials?

MM If a patient has a GLOBE score of less than -0.8, that person has an excellent survival without doing anything other than taking ursodeoxycholic acid. If a new agent is being tested in addition to ursodeoxycholic acid, patients with a GLOBE score greater than -0.8 should be targeted.

G&H Do all patients fit the prognostic curve of this score?

MM No, that is the main problem with population-based survival scores; an individual patient might not fit the curve perfectly. A patient may be told that he or she can expect a complication-free life with a certain degree of certainty, but nothing is guaranteed. For example, if a patient has a GLOBE score of less than -0.8, that person can be reassured that there is a 98% chance of transplant-free survival at 5 years and a 93% chance at 10 years, which are fairly good statistics. However, patients with a GLOBE score greater than -0.8 have a 42% risk of mortality at 10 years without a transplant, which is a significantly increased risk of death.

G&H How does the GLOBE score compare with previous scores for PBC?

MM The C-statistic (a measure of how well a test performs) for the GLOBE score was .81 in the derivation

cohort and .80 in the validation cohort, whereas the C-statistics for the other scores (including the Mayo risk score, Rotterdam criteria, Paris 1 criteria, Paris 2 criteria, Toronto criteria, and Barcelona criteria) ranged from .57 to .70. Therefore, the GLOBE score was quite a bit more accurate at predicting transplant-free survival.

G&H What are the main advantages and disadvantages of the GLOBE score?

MM One of the main advantages is that the score uses readily available data that the average clinician has on a patient. Another is that the score provides the most accurate prognostic information possible.

One disadvantage is that the control group was not international; it came from just one country (the Netherlands). Another disadvantage is that the formula is too complex for physicians to calculate in their head; calculation of the score requires a phone app or online help.

G&H Can the score be used in all patients with PBC?

MM I believe so because it was tested in the broadest group of PBC patients possible; virtually no patients for whom data were available were excluded. Therefore, the results should be broadly applicable, more so than any of the previous scores that have been published.

G&H What are the next steps in research in this area?

MM A number of promising new agents are entering the arena for clinical trials in PBC, and the GLOBE score will be helpful for identifying the population that should be enrolled in these studies and, just as importantly, identifying the population that does not need to be enrolled in these studies. As these trials incorporate the GLOBE score, it will be interesting to see whether the score can be used as a surrogate marker of success for these therapies.

The GLOBE study was funded by Intercept Pharmaceuticals. Dr Mayo has received grant support from Intercept Pharmaceuticals in the past to conduct clinical trials.

Suggested Reading

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