ADVANCES IN HEPATOLOGY

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The Possible Effects of Ursodeoxycholic Acid on Recurrent Primary Biliary Cholangitis and Biliary Complications After Liver Transplant

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G&H What are the effects of ursodeoxycholic acid when used as first-line treatment for primary biliary cholangitis, and how often does adequate response to this treatment occur?

MP Several randomized controlled trials and analyses have shown that ursodeoxycholic acid (UDCA) delays histologic progression and prolongs transplant-free survival in patients with primary biliary cholangitis (PBC). Response to UDCA at 1 year gives a sense of how patients will do, with response defined as improvement in alkaline phosphatase. Although the exact cutoff may vary from study to study, a serum alkaline phosphatase of less than twice the upper limit of normal is a good predictor of treatment response.

Adequate response to UDCA occurs in approximately 60% of patients with PBC, which means that it does not occur in 40% of patients. Without adequate response, the median transplant-free survival at 10 years is approximately 50% to 70% in asymptomatic patients and lower in symptomatic patients. With adequate response, survival is fairly similar to that of an average person.

G&H When is liver transplant indicated for the treatment of patients with PBC, and what are the typical outcomes?

MP The indications for liver transplant for PBC are very similar to those for other chronic diseases. Thus, evaluation typically begins when patients develop decompensated liver disease or when they have a Model for End-Stage Liver Disease (MELD) score of 15 or greater or a bilirubin of more than 6 mg/dL. Historically, MELD exceptions have been granted in very select cases when patients have severe intractable pruritus that is unresponsive to any of the treatment options that are currently available.

Outcomes for patients with PBC have historically been more favorable than for other disease categories, such as hepatitis C virus infection and alcohol-related liver disease. Studies have shown 1- and 5-year survival rates of 90.2% and 84.0%, respectively, although these data are approximately 10 years old now.

G&H How common are biliary complications and recurrent PBC following liver transplant?

MP In the general liver transplant population, the incidence of biliary complications has ranged widely in the literature, from 10% to 25%. Breaking this down, the incidence of strictures has ranged between 4% and 16%, and the incidence of stones and sludge has ranged from 2.5% to 12%. I am unaware of any data suggesting that

the incidence of these biliary complications is different in liver transplant recipients with PBC.

As far as recurrent PBC after liver transplant, it has historically been published that at 10 years, PBC will recur in up to 30% to 35% of patients. These estimates match findings from the meta-analysis that my colleagues and I recently published.

G&H What has the research to date found about the possible effects of UDCA on biliary complications and recurrent PBC after liver transplant?

MP A randomized controlled trial looking at the use of UDCA after liver transplant in the general liver transplant population found a decrease in the incidence of biliary sludge and casts, but the overall rates of biliary strictures, complications, and survival were similar. A case-control study from 2008 found that the overall incidence of bile duct stones and casts was approximately 3.8%. This study also found that UDCA had a significant effect in preventing the development of post-transplant bile duct stones.

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The data on UDCA's effects on recurrent PBC have been limited in terms of 2-armed studies (ie, having an arm with UDCA and an arm without UDCA), and have mainly consisted of single-center, retrospective case series. However, one of these 2-armed studies examined preventive UDCA use in 90 patients across 4 centers in Europe, and found a decreased rate of recurrence of PBC, down to 11% at 5 years and 40% at 15 years. In contrast, a review of 312 patients from the Japanese Liver Transplant Society database did not show UDCA to have any significant effect on the rates of recurrent PBC. Both of these studies had overlapping confidence intervals in the rate of recurrence.

G&H What were the findings of your own research in this area?

MP My colleagues and I recently performed 2 separate meta-analyses. For total biliary complications, we were able to pool the outcomes of 3 studies that found an overall odds ratio of 0.43 for stones and sludge, which drove an odds ratio of 0.57 for a composite biliary complications endpoint. There was no significant difference in the odds of biliary strictures in patients on UDCA. This finding was not completely unexpected, as the incidence of biliary strictures is affected more by surgical and technical issues.

For recurrent PBC, we pooled 12 studies, which consisted of a total of 1727 patients and which had a follow-up of at least 3 years. We found a pooled PBC recurrence rate of 16.7% in patients on UDCA and 23.1% in patients without UDCA. This trend persisted when we limited the studies to those with at least 9 years of follow-up; the pooled PBC recurrence rate was 13.3% in patients on UDCA and 33.8% in patients without UDCA.

Coincidentally, around the time that our meta-analyses were being published, Corpechot and colleagues at the Global PBC Study Group published similar findings in terms of the rate of recurrence of PBC. In a retrospective study of 780 patients from their database, the researchers found a decrease in the rate of recurrent PBC as well as decreases in the rates of graft loss and all-cause mortality in patients who were kept on UDCA after liver transplant.

G&H Are there any limitations in your research that should be taken into account?

MP We had limitations in both of our meta-analyses. The 3 studies that we were able to find that had both UDCA and non-UDCA arms for our meta-analysis on biliary complications had very different designs. One was a retrospective cohort study, another was a randomized controlled trial, and the third was a case-control study with a prematched set of patients without biliary complications. Thus, it is difficult to group all of these studies together, and in the end, there were only approximately 530 patients. It was this paucity of data and the unclear effect of UDCA on biliary complications after liver transplant that motivated us to perform this meta-analysis in the first place.

As for our meta-analysis on recurrent PBC, we found only 2 studies that had both UDCA and non-UDCA arms. We ended up calculating pooled recurrence rates instead of odds ratios. By making that shift, we were

able to include 12 studies with 1727 patients in total, although most of these studies were mainly retrospective, single-center case series. Fortunately, the diagnosis of recurrent PBC varied very little from site to site, with a compatible liver biopsy in the setting of cholestatic liver chemistries required to make the diagnosis.

G&H Is it known why UDCA might have prophylactic effects on recurrent PBC or biliary complications?

MP This is difficult to answer because it is still unknown what exactly causes PBC. Nonetheless, UDCA is known to have multiple effects on patients with PBC, including increasing the hydrophilicity of bile, promoting the insertion of the bile salt export protein into the canalicular membrane, and improving the function of anion exchange protein 2 to secrete bicarbonate into the bile canaliculi. All of these effects decrease the exposure of hepatocytes and biliary epithelial cells to toxic bile acids. When UDCA is given in a prophylactic manner, these effects may protect against the original cholangiocyte injury and resultant autoimmunity.

> … according to our research, 50 patients would need to be treated to prevent 1 biliary complication.

In addition, UDCA is known to have litholytic properties. It decreases the secretion of cholesterol and can help reduce the rate of biliary stones and sludge, even in patients who have not undergone liver transplant; therefore, it is not surprising that UDCA would produce such effects in liver transplant recipients as well. However, strictures are less affected by the content of the bile than by technical and surgical issues that arise at the time of liver transplant.

G&H Are there any drawbacks to using UDCA in liver transplant recipients?

MP There are very few medical drawbacks. UDCA is a generally well-tolerated drug with few, if any, side effects. The primary considerations are the cost and the patient burden of taking additional medication. UDCA is often one of 8 to 10 medications that a patient may be taking initially after transplant. In addition, it should be noted that the number needed to treat to prevent biliary complications can be high. For example, the research that my colleagues and I conducted showed an overall odds ratio of approximately 0.4. If the baseline incidence of bile stones and sludge is 5%, then the incidence on UDCA prophylaxis is 3%. Thus, according to our research, 50 patients would need to be treated to prevent 1 biliary complication.

For recurrent PBC, the drawbacks are similar, with the exception that the number needed to treat is quite different. Based on the 12 studies in our meta-analysis, the number needed to treat is approximately 15. However, looking only at studies with at least 9 years of follow-up, the number needed to treat is only 5.

G&H Is there consensus yet on whether UDCA should be used in all patients with PBC after they have undergone liver transplant?

MP There is no society recommendation for the universal use of UDCA for PBC after liver transplant. However, with the recent meta-analysis that my colleagues and I performed as well as the recent study from the Global PBC Study Group, I think that consensus is building that UDCA, dosed at 13 to 15 mg/kg indefinitely, yields a substantial benefit in the reduction of recurrent PBC and mortality in patients with PBC who have undergone liver transplant. I believe that the use of UDCA will become more and more common in this patient population.

As for the general liver transplant population, I would advocate for a more targeted approach for UDCA therapy, as universal prophylaxis may not be beneficial to all patients. UDCA, again at a dose of 13 to 15 mg/kg, should be considered in all liver transplant recipients who have an increased risk of biliary complications, including patients with known biliary strictures or a history of biliary stones, patients with ischemic complications, and patients who had living donors.

G&H What other agents can be used alone or in combination with UDCA to help prevent recurrent PBC or biliary complications after liver transplant?

MP For biliary complications, no other prophylactic agents are currently available. Cyclosporine has been found to be superior to tacrolimus in preventing recurrent PBC, and the effect of cyclosporine may be improved by using it in combination with UDCA. However, the benefits of using cyclosporine need to be weighed against

the increased risk of rejection in patients who are not on tacrolimus.

G&H What research is still needed in terms of the use of UDCA after liver transplant?

MP A prospective study would better answer the question of whether UDCA prevents recurrent PBC. Having said that, given the relative rarity of PBC and the long-term follow-up required, such a study would need to be a long-term, multicenter study, which may be difficult to both coordinate and fund.

Disclosures

Dr Pedersen has no relevant conflicts of interest to disclose.

Suggested Reading

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