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Use of Obeticholic Acid in Patients With Primary Biliary Cholangitis

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G&H Why was there a need for a treatment option in addition to ursodeoxycholic acid for patients with primary biliary cholangitis?

RB Many primary biliary cholangitis (PBC) patients who have been on ursodeoxycholic acid (UDCA) for months to even years have an inadequate response (defined as lack of normalization of alkaline phosphatase [ALP]). Large longitudinal studies have shown that such a response is associated with greater degrees of histologic progression. In the Global PBC Study, approximately 40% of patients had an elevated risk of disease progression owing to insufficient response of their ALP to UDCA therapy. PBC patients should thus be monitored for their response to treatment every 3 to 6 months. Bilirubin is also an important predictor of survival. Once bilirubin is over 3 mg/dL, it is very difficult for disease to improve with treatment other than liver transplantation. Thus, if patients have a poor response to UDCA, the need for liver transplantation and the likelihood of disease progression increase. It stands to reason that if another agent would lower ALP when added to PBC treatment, outcomes would likely improve.

G&H What is obeticholic acid?

RB Obeticholic acid (Ocaliva, Intercept Pharmaceuticals) recently received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of PBC in combination with UDCA in adult patients who have an inadequate response to UDCA, or as monotherapy in adult patients who are intolerant of UDCA. This approval was not based on histology but on improvement in ALP because the FDA recognized that a study to demonstrate histologic improvement would take a long time and there was an unmet medical need for therapy for the aforementioned 40% of UDCA nonresponders.

G&H What is the mechanism of action of obeticholic acid?

RB UDCA and obeticholic acid are both synthetic bile acids, and have complementary mechanisms of action. Obeticholic acid is a farnesoid X receptor (FXR) agonist that is active in a wide variety of pathways. It decreases bile acid synthesis, resulting in less buildup of toxic bile acids and less cholestatic damage. At the same time, it also increases bile acid secretion. Both obeticholic acid and UDCA have choleretic effects, causing more bile acid flow, less buildup of toxic bile acids in the liver parenchyma, as well as less inflammation and direct cell damage. In addition, because FXR regulates both inflammation and fibrosis, obeticholic acid has both anti-inflammatory and antifibrotic properties. UDCA is a more hydrophilic, less-toxic bile acid that replaces the bile acid pool, leading to less indirect damage, and obeticholic acid increases bile acid secretion. Used together, these agents improve liver

Table. Percentage of Patients Achieving the Components of the Primary Composite Endpoint at Month 12[a]

	Obeticholic Acid 5 mg to 10 mg Titration + UDCA (n=70)	Obeticholic Acid 10 mg + UDCA (n=73)	Placebo + UDCA (n=73)
ALP <1.67 × ULN	47%	55%	16%
ALP decrease of ≥15%	77%	78%	29%
Total bilirubin ≤ ULN	89%	82%	78%

[a]16 patients (7%) who were intolerant did not receive concomitant UDCA.

ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Adapated from Ocaliva [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2018.

test results more than UDCA alone in patients who are failing UDCA.

G&H What data have been reported on obeticholic acid from POISE?

RB POISE was a randomized, double-blind, placebo-controlled, 3-arm study in PBC patients who had an inadequate response to UDCA or were intolerant of the drug. Inadequate response was defined as an ALP at least 1.67 times the upper limit of normal (ULN) and/or a bilirubin greater than the ULN but less than 2 times the ULN. The majority of patients were entered into the study based on ALP, and over 90% of the patients were already on UDCA and continued on it. Thus, the placebo arm was not a true placebo; it was essentially UDCA monotherapy being compared to either 10 mg of obeticholic acid, or dose titration in which patients received 5 mg for the first 6 months and, if they did not achieve the primary endpoint, were rerandomized to either stay on 5 mg or go up to 10 mg.

The primary composite endpoint was an ALP below 1.67 times the ULN and a decrease of at least 15% in ALP, with a normal bilirubin. Because most of the patients already had a normal bilirubin, the endpoint was predominately based on a substantial lowering of ALP. The composite endpoint was achieved by only approximately 10% of the UDCA plus placebo group but by approximately 46% of the obeticholic acid dose-titration group and 48% of the obeticholic acid 10-mg group. The Table shows the percentage of patients who achieved the various components of the primary composite endpoint at month 12. Close to 80% of obeticholic acid patients had a 15% or more drop in their ALP.

Taking patients intolerant to UDCA from this trial and combining them with such patients from prior trials, approximately 40% achieved the endpoint with obeticholic acid monotherapy, suggesting that patients had the same response to obeticholic acid regardless of whether they did not respond to UDCA or did not take UDCA. In those studies, the mean reduction of ALP in patients who were not on UDCA was a drop of almost 250 U/L. At the beginning of POISE, the mean ALP was between 300 and 350 U/L. (Patients had to be above approximately 200 U/L to be in the study.) ALP decreased in both the 5- and 10-mg groups in the first 3 months. At 6 months, rerandomization occurred. By the end of 12 months, the dose-titration group and the 10-mg group achieved similar reductions in ALP, whereas in the placebo arm, there was only a little reduction with no real substantial change over 1 year. Although bilirubin was normal in most patients, it still decreased with obeticholic acid likely because the drug is a choleretic. A drop is also seen when UDCA is started. In contrast, bilirubin does not drop with placebo over time; if anything, it rises.

G&H Why was dose titration used in POISE?

RB In patients who did not achieve a response at 6 months, increasing the dose from 5 mg to 10 mg at that time resulted in added benefit in terms of achieving the primary endpoint. Uptitration allows patients to receive the minimum dose that they need and, as a result, minimizes side effects while still maintaining the same degree of efficacy. According to the FDA, uptitration of obeticholic acid can occur as early as 3 months (not 6 months as performed in the trial) because between 3 and 6 months in POISE, the ALP essentially plateaued without further decreases.

G&H How significant of a concern is hepatic decompensation with obeticholic acid?

RB There have been postmarketing reports of hepatic decompensation in PBC patients with Child-Pugh Class B and C cirrhosis who were taking obeticholic acid. However, the majority of these patients were given incorrect dosing. Patients with hepatic decompensation

(Child-Pugh B or C) should receive lower doses because obeticholic acid is metabolized by the liver and, thus, can accumulate when there is liver dysfunction. Therefore, for patients with Child-Pugh Class B and C or decompensated cirrhosis, the dose should be 5 mg once weekly, whether the patients are currently decompensated or have had a decompensating event in the past.

If patients get beyond month 3 without pruritus, the side effect is unlikely to occur.

The timing of hepatic decompensation tended to occur very early (in the first month or so) and was characterized by a rise in bilirubin. Thus, any PBC patient started on obeticholic acid who experiences an increase in bilirubin should undergo investigation to determine why it is occurring. As usual, imaging should be performed to look for biliary obstruction. Then, physicians should consider which medications the patient is taking. If the patient is on obeticholic acid, the dose should be decreased to weekly or the drug should be held until the patient improves. Other potential agents that could cause drug-induced liver injury should also be assessed and infection and other causes excluded. Patients with decompensated cirrhosis should start at 5 mg once weekly. Titration is based on inadequate response (defined solely on ALP, not on elevated bilirubin). The maximum dose for patients with decompensation should be 10 mg twice weekly, given 3 days apart.

G&H Are there any contraindications to the use of this drug?

RB The main contraindication is biliary obstruction. Extra bile salts should not be given to a patient with biliary obstruction. If a patient has a biliary obstruction, obeticholic acid should be stopped and the obstruction should be relieved.

G&H How common is pruritus in patients taking obeticholic acid, and when does it tend to occur?

RB Pruritus is the defining symptom of PBC and side effect of obeticholic acid. Approximately 60% of patients in POISE had a prior history of pruritus. In clinical trials, approximately 20% of patients had what they considered to be severe pruritus (defined as intense or widespread itching that was interfering with their daily life or sleep and that typically required medical intervention). The number of patients with severe pruritus in the obeticholic acid–treated arms was a little more than approximately twice the number in the placebo arm. Discontinuations for pruritus were higher in patients who started at 10 mg than those who started at 5 mg and titrated up to 10 mg (10% vs 1%, respectively).

As with decompensation, pruritus tended to occur early. Thus, patients can be reassured that if they start on obeticholic acid, they will know early on whether there is a problem, and then it can be managed. If patients get beyond month 3 without pruritus, the side effect is unlikely to occur.

G&H How can pruritus be managed if it occurs?

RB Managing pruritus in liver disease patients is always a challenge, as there is no completely effective therapy currently available. Antihistamines are one option, but they do not work well in liver disease; they mainly help by sedating patients at night. I use doxepin 5 to 10 mg at bedtime far more frequently because I think it helps more. Bile acid resins do work, but they are challenging because patients do not like taking them and because they have to be taken 4 hours apart from both obeticholic acid and UDCA (the latter 2 of which can be taken together). In addition, bile acid resins may result in changes in the international normalized ratio in patients on warfarin, which should be monitored. Another option for managing pruritus is reducing the dose of obeticholic acid and, in the case of severe pruritus that is greatly interfering with patients, taking a dose holiday with or without trying to restart at a lower dose. Simple measures can also be helpful for patients with pruritus, such as keeping the skin moist, wearing cotton clothing, avoiding hot showers, and using colloidal oatmeal.

G&H Are there any other side effects with obeticholic acid?

RB Pruritus is the main side effect. The rest of the side effects are minor, common symptoms that may occur over the course of a year (eg, fatigue, abdominal pain, rash, dizziness, constipation), and may or may not be related to the drug. However, any medication may cause minor symptoms, and patients should report any symptoms to their physician. Nonpruritus-related discontinuations were approximately the same in the drug-treated arms as in the placebo arm. Of the patients who finished 12

months of treatment, 97% chose to continue in the open-label extension. Thus, this drug is very well-tolerated.

G&H Are there any potential drug interactions associated with this agent?

RB Obeticholic acid is not metabolized through cytochrome (CYP) 3A4B, so although there is no need to worry about interacting with drugs with typical CYP450 activity, obeticholic acid may increase exposure to CYP1A2 substrates, which have a narrow therapeutic index. Thus, obeticholic acid will increase the levels of theophylline and tizanidine but not other classes of drugs.

Obeticholic acid is also an inhibitor of bile salt efflux pump, which is important in cyclosporine transport. There is no posttransplant indication for this drug, so patients should not take cyclosporine, but tacrolimus and other immunosuppressive drugs are not expected to have substantial drug-drug interactions.

G&H How should lipids be managed in patients taking obeticholic acid?

RB Patients with PBC have disordered lipid profiles, usually marked by high total cholesterol and disproportionately elevated high-density lipoprotein (HDL). This leads to controversy in the hepatology community as to the actual cardiac risk profile for PBC patients, although their risk is lower than other patients with similar elevations of total cholesterol. With obeticholic acid, a reduction is seen in HDL-cholesterol in the dose-titration and 10-mg groups early on, and more frequently than in the placebo arm. However, clinically significant reductions in HDL-cholesterol are fairly low because the levels are so high at the start of treatment. Physicians should monitor lipids in all patients with PBC and certainly any patients who are on obeticholic acid. I usually do it every 3 months in the beginning and then eventually every 6 months.

G&H Should any other monitoring or dosing information be kept in mind when managing these patients?

RB It is important to monitor all PBC patients regularly, particularly those with cirrhosis. If their liver disease is progressing, physicians should either reduce the dosing of the drug, or, if the change in liver tests may be drug-related, stop the dosing and reassess. The more advanced the liver disease, the more physicians should monitor the patients. Patients on the transplant list are monitored every 3 months, and patients with compensated cirrhosis should be monitored at least every 3 months for the first 6 months and after that at least every 6 months. Physicians should consider stopping treatment if the bilirubin rises or the liver decompensates.

It is also important to keep in mind that the younger the patient and the more advanced the disease, the lower the threshold should be to try to modulate the disease activity. However, each treatment decision should be individualized to the patient and his or her individual risk-benefit assessment, including the HDL, the degree of pruritus at baseline, and the response to UDCA.

G&H How is insurance coverage of obeticholic acid?

RB Generally, this drug requires prior authorization, but the manufacturer has a program to help patients with the process. Most patients receive approval, regardless of whether their ALP is above or below 1.67 times the ULN, as long as their physician defines them as inadequate responders or as being intolerant of UDCA, and documents that well in their chart.

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Suggested Reading

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