Obeticholic Acid in Primary Biliary Cholangitis

TO THE EDITOR: Nevens et al. (Aug. 18 issue) highlight the efficacy and safety of obeticholic acid in patients with primary biliary cholangitis. The inclusion of a trial with a short follow-up of 1 year for a disease with an estimated duration of one to two decades without intervention certainly dilutes the information that is needed for the analysis of clinically relevant outcomes. Appropriate criteria that define the treatment duration and response with new regimens for primary biliary cholangitis are unknown. The use of surrogate end points such as a reduction in the level of alkaline phosphatase alone as a measure of clinical improvement during treatment with obeticholic acid, despite no change in liver fibrosis variables, is debatable. Moreover, a long-lasting effect of 12 months of obeticholic acid on the rate of disease progression is unknown.

Data are limited with regard to the benefit of obeticholic acid in patients at utmost need — those with advanced-stage primary biliary cholangitis. Only approximately 20% of the patients had a liver-stiffness measurement of 16.9 kPa or more, and almost 50% had missing liver-stiffness values. Patients with primary biliary cholangitis present with pruritus, and the worsening of pruritus during treatment with obeticholic acid would be undesirable.2 It is advisable that no recommendations be made on the basis of the present trial until long-term prospective studies including all stages of primary biliary cholangitis are conducted to validate these associations.

Ankur Jindal, M.D., D.M.
Institute of Liver and Biliary Sciences
New Delhi, India
ankur.jindal3@gmail.com

Aditi Gupta, M.D.
Healthfirst Polyclinic
New Delhi, India

Shiv Sarin, M.D., D.M.
Institute of Liver and Biliary Sciences
New Delhi, India

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1611913

TO THE EDITOR: One aspect of the PBC OCA International Study of Efficacy (POISE) deserves further clarification. As obeticholic acid increases plasma levels of mitogenic fibroblast growth factor 19 (FGF-19) by targeting intestinal farnesoid X receptor (FXR), it may have unwanted effects on comorbid or incipient cancers. Preliminary data indicate that FGF-19 may advance the growth of certain hepatocellular carcinomas as well as breast, lung, and prostate cancers. However, the trial protocol remains vague about the exclusion of patients who are at risk for or who have received a diagnosis of a nonhepatobiliary cancer. It is striking that a known cancer is not listed under key exclusion criteria but is categorized as a disorder that may diminish life expectancy to less than 2 years (see the protocol, available with the full text of the article at NEJM.org). On the basis of this statement, it is unclear whether or how the oncologic profile of the trial participants was assessed and which cancers at which stage were considered to be acceptable for inclusion. This aspect is particularly important because the safety of prolonged treatment with obeticholic acid was a main aim of the trial.

Rowan F. van Golen, M.Sc.
Academic Medical Center
Amsterdam, the Netherlands
r.f.vangolen@amc.nl

No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: Nevens et al. state that obeticholic acid administered with ursodiol or as monotherapy significantly improved biochemical variables in patients with primary biliary cholangitis. They further state that obeticholic acid and ursodiol have “distinct but complementary pharmacologic properties.” However, Nevens et al. miss opportunities to evaluate the latter claim, and clinicians are left without trial data to know whether these medications are indeed complementary.

The majority of participants were treated with both agents, whereas only 11 received obeticholic acid monotherapy. Unfortunately, the authors do not report whether the participants who took ursodiol had a partial response or no response and whether these factors affected the responsiveness (or lack thereof) to obeticholic acid.

These missed opportunities are important because, as noted by Pratt in his accompanying editorial,1 patients can have a variety of responses to ursodiol. Further characterization is needed to determine the best strategy for using this new medicine.

Lisa A. Spacek, M.D., Ph.D.
Johns Hopkins University
Baltimore, MD

Steven F. Solga, M.D.
University of Pennsylvania
Philadelphia, PA
steven.solga@uphs.upenn.edu

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1611913

THE AUTHORS REPLY: The surrogate biochemical end points that were evaluated in POISE are biologically relevant markers of cholestasis that are reflective of the underlying pathophysiological characteristics of primary biliary cholangitis. Clinical studies that have been conducted across the globe and two large, independent clinical databases, the Global PBC Study Group and the U.K.—PBC Consortium, have shown that alkaline phosphatase and bilirubin, which are closely related to the pathogenicity of the disease, are strongly predictive of an adverse clinical outcome.1,2 However, we agree that clinical outcomes are ultimately the end points of greatest interest, although such trials take a long time to execute in rare diseases. A large international trial evaluating clinical outcomes, together with other secondary end points such as liver stiffness, in patients with advanced disease is currently ongoing (COBALT ClinicalTrials.gov number, NCT02308111).

Obeticholic acid treatment in addition to ursodiol increased FGF-19 levels, with corresponding reductions in endogenous bile acid levels. Although it has been proposed that FGF-19 (and its homologue fibroblast growth factor 15 [FGF-15] in rodents) have oncogenic potential, a recent physiologically relevant study has addressed the relationship between FGF-15 and hepatocarcinogenesis in FXR-knockout mice, in which hepatocellular tumors spontaneously develop.3 Selective intestinal FXR reactivation in these mice restored the FGF-15–cholesterol 7-alpha-hydroxylase enterohepatic axis and protected against hepatocellular carcinoma.3

Since 93% of the patients were taking stable doses of ursodiol before and throughout our trial, the pharmacologic effects we observed were additive. Although each patient's biochemical values before the initiation of ursodiol were not obtained to allow the precise determination of each patient's response to ursodiol, the pretrial baseline biochemical values identified the patients as having an increased risk of adverse clinical outcomes, and therefore, by this definition, they had an inadequate response to ursodiol.

Frederik Nevens, M.D., Ph.D.
University Hospitals KU Leuven
Leuven, Belgium
frederik.nevens@uzleuven.be

Keith D. Lindor, M.D.
Arizona State University
Tempe, AZ

David E. Jones, M.B., B.Chir., Ph.D.
Newcastle University Medical School
Newcastle upon Tyne, United Kingdom

Since publication of his article, Dr. Nevens reports receiving fees for serving on an advisory board from Intercept Pharmaceuticals. No further potential conflict of interest was reported.


DOI: 10.1056/NEJMc1611913

Correspondence Copyright © 2016 Massachusetts Medical Society.