This year’s European Association for the Study of the Liver (EASL) International Liver Congress, held from April 19 to 23 in Amsterdam, hosted approximately 10,000 specialists from around the world to present, share, and debate the latest science and research in hepatology. We review below key sessions on cirrhosis, hepatitis C virus infection, primary biliary cholangitis, and hepatocellular carcinoma.

Long-Term Albumin Administration Improves Survival in Patients With Decompensated Cirrhosis: Final Results From the ANSWER Study

- Mauro Bernardi, MD, University of Bologna, Bologna, Italy

Long-term administration of albumin in patients with cirrhosis and ascites improves survival and quality of life, according to the investigator-initiated ANSWER study.

Although it is expensive to produce, albumin is available from several commercial sources, and pricing has remained generally stable since albumin’s utility as a plasma expander was recognized in World War II. Among human albumin’s many other roles, it plays an important one in regulating the body’s fluid distribution. Human albumin has long been used in the acute setting to treat severe complications of cirrhosis. However, persistent questions about albumin’s long-term utility, Dr. Bernardi said in an EASL press conference, have remained unstudied because albumin is not patentable.

Dr. Bernardi noted that liver cirrhosis accounts for 1.8% of all deaths annually in Europe, which the World Health Organization estimates at 170,000 per year. Decompensated cirrhosis marks the symptomatic stage of the disease, with ascites as the most common first event. Cirrhosis, after decompensation, becomes a systemic disease with multiorgan dysfunction and failure. Low levels of serum albumin are common in cirrhosis patients. Mortality in the first year after decompensated cirrhosis occurs is about 20%, and liver transplantation is the only curative therapy.

ANSWER investigators enrolled 440 patients with cirrhosis and uncomplicated ascites who had been treated at least minimally with an anti-mineralocorticoid drug (200 mg per day) plus furosemide (25 mg per day). They were prestratified according to the need for paracentesis in the prior month. Patients were randomized 1:1 to 18 months of standard medical treatment (SMT) (which could include albumin according to standard indications) or SMT plus human albumin 40 g twice weekly for two weeks followed by 40 g per week for the remainder of the trial. The ANSWER primary endpoint was overall survival (OS).

Dr. Bernardi reported that after 18 months the need for paracentesis was reduced significantly in the albumin-added group compared with the SMT group (38% versus 66%, respectively; \( P < 0.001 \)). The cumulative paracentesis incidence rate (per person, per year) was 3.50 (95% confidence interval [CI], 3.1–3.8) in the SMT group. The incidence-rate ratio (IRR) for the human albumin-added group versus the SMT group was 0.46 (95% CI, 0.40–0.53; \( P < 0.0001 \)), indicating a 54% reduction in paracentesis with the addition of human albumin. OS, the primary endpoint, was 66% in the SMT group and 78% in the human albumin-added group (hazard ratio [HR], 0.62; 95% CI, 0.40–0.95; \( P = 0.0285 \)), a 38% hazard reduction.

Among secondary endpoints, a 45% reduction in cumulative days in the hospital was also significant. In the SMT group, the incidence rate of cumulative hospital days reached 19.4 [95% CI, 18.7–20.1] and the IRR for the human albumin-added group versus the SMT group was 0.55 (95% CI, 0.52–0.58; \( P < 0.0001 \)). Significant benefits also accrued to the human albumin-added group for general ascites management, cirrhosis complications, and quality of life. Treatment was generally well tolerated with four acute events from which all patients recovered (with two study interruptions).

Commenting on the ANSWER findings, EASL Governing Board Member Annalisa Berzigotti, MD, from the University Clinic for Visceral Surgery and Medicine at the University of Berne in Switzerland, said: “The reduction in mortality observed in the albumin-treated arm of this randomized controlled study is a novel and important piece of information. Based on this data, weekly administration of albumin should be considered in patients with cirrhosis and ascites to prevent life-threatening complications.”

ENDURANCE-3: Safety and Efficacy Of Glecaprevir/Pibrentasvir Compared With Sofosbuvir Plus Daclatasvir in Treatment-Naïve HCV Genotype 3

- Graham Foster, MD, Queen Mary University of London, London, United Kingdom

“While there has been great progress made in the treatment of patients with hepatitis C, there remain limited options for those with genotype 3 disease,” Dr. Foster stated at an EASL press briefing. He noted that among the 15 million people in the European Union with hepatitis C virus (HCV) infection, those with genotype 3 (GT3) disease are the most difficult to cure.

Chronic HCV GT3 infection is common and progressive, with particular prevalence among intravenous drug users. Rates of sustained virological response (SVR) with direct-acting antiviral (DAA) therapies are reduced in GT3 patients. The EASL-recommended regimens for treatment-naïve patients without cirrhosis are sofosbuvir (Sovaldi, Gilead Sciences) plus daclatasvir (Daklinza, Bristol-Myers Squibb) (SOF + DCV) for 12 to 24 weeks and sofosbuvir/velpatasvir (Epclusa, Gilead Sciences) for 12 weeks. Shorter treatment duration, Dr. Foster said, could enhance patient adherence and access to treatment.
MEETING HIGHLIGHTS: EASL International Liver Congress 2017

ENDURANCE-3, a phase 3, open-label, active-controlled study, compared the investigational combination of glecaprevir/pibrentasvir (300 mg/120 mg) with SOF + DCV. Glecaprevir, a pangenotypic NS3/4A protease inhibitor, and pibrentasvir, a pangenotypic NS5A inhibitor, are next-generation DAAs. Their coformulation (G/P) allows once-daily oral dosing. In prior phase 2 and 3 studies, G/P administered for eight weeks in treatment-naïve GT3 patients without cirrhosis led to 97% of patients having undetectable HCV for 12 or more weeks after the end of treatment (SVR12) with no virological failures. In part 3 of the SURVEYOR-II trial, 12 weeks of treatment in GT3 patients with cirrhosis led to a 98% SVR12 rate.

The objective of the ENDURANCE-3 study was to determine the efficacy and safety of G/P in noncirrhotic treatment-naïve patients with HCV GT3 using a comparison of SVR12 (non-inferiority) with either 12 weeks of G/P (n = 233) or SOF + DCV (n = 115). A third arm of the trial included 157 patients receiving G/P for eight weeks, which was compared for noninferiority with 12 weeks of G/P.

Mean age was approximately 48 years, and intravenous drug use history was positive in about 64% of the patients. Intent-to-treat analysis for 12 weeks of treatment revealed similar SVR12 rates of 95% for G/P and 97% for SOF + DCV. In the group of patients treated with G/P for eight weeks, the SVR12 rate was 95%. “Both G/P treatments met noninferiority criteria for the primary endpoint,” Dr. Foster said. Reporting further on virological failures, he noted one virological breakthrough in each of the G/P groups, and three, one, and five relapses occurred in the G/P 12-week, SOF + DCV, and G/P eight-week groups, respectively.

No serious adverse events were related to the study drugs, and discontinuation rates for adverse events were low at 1% for both 12-week regimens and 0% for the eight-week regimen.

“Glecaprevir/pibrentasvir (300 mg/120 mg) was well tolerated, with a safety profile comparable to SOF + DCV. G/P achieved high efficacy in noncirrhotic treatment-naïve patients with chronic HCV GT3 infection,” Dr. Foster concluded. “Treatment with this once-daily regimen for eight weeks could provide a highly efficacious and well-tolerated option for treatment-naïve noncirrhotic patients with hepatitis C, genotype 3, if approved by the regulatory authorities.”

Ledipasvir/Sofosbuvir With or Without Ribavirin For 12 or 24 Weeks Is Safe and Effective in Children 6 to 11 Years Old With HCV Infection

• Karen F. Murray, MD, Seattle Children’s Hospital, Seattle, Washington

A clinical trial of ledipasvir/sofosbuvir (LDV/SOF) (Harvoni, Gilead Sciences) with or without ribavirin suggests that there is a new well-tolerated treatment option for children 6 to 11 years of age with chronic hepatitis C virus (HCV) infection.

Dr. Murray noted that the estimated prevalence of HCV infection in children is up to 0.4% in Europe and the United States and up to 6% in resource-limited countries. Vertical transmission is the usual etiology. While direct-acting antivirals (DAAs) have transformed the treatment of adults with chronic HCV, the standard of care for children younger than 12 years of age remains pegylated interferon plus ribavirin for 24 to 48 weeks, a regimen that causes severe side effects. For children 12 years of age and older (or those weighing 35 kg or more), sofosbuvir (Sovaldi, Gilead Sciences) and LDV/SOF have recently been approved, and a half-strength, single-tablet, fixed-dose combination for younger children has recently been developed.

Dr. Murray’s ongoing open-label study included 90 children 6 to 11 years of age with chronic HCV infection. Most (n = 86) had genotype 1 infection and received 12 weeks of treatment with LDV/SOF (45 mg/200 mg). One child who had cirrhosis and had failed prior treatment with pegylated interferon and ribavirin received 24 weeks of treatment. Genotype 3 patients (n = 2) received LDV/SOF plus ribavirin for 24 weeks. Genotype 4 patients (n = 2) received LDV/SOF for 12 weeks. The primary endpoint was the rate of sustained virological response defined as undetectable HCV for 12 or more weeks after the end of treatment (SVR12).

Most of the children were boys (59%), white (79%), treatment-naïve (80%), and vertically infected (97%).

Among children receiving 12 weeks of LDV/SOF, 99% achieved SVR12. The remaining children receiving 24 weeks of LDV/SOF with or without ribavirin also achieved SVR12. One GT1a patient with cirrhosis relapsed.

The most common side effects reported in 10% or more of patients were headache, fever, abdominal pain, diarrhea, vomiting, cough, fatigue, sore throat, and nausea. There were no grade 3 or 4 adverse events and no treatment discontinuations due to adverse events.

“In GT1-, 3-, or 4-infected patients 6 to 11 years old, a single-tablet regimen of LDV/SOF 45 mg/200 mg with or without ribavirin for 12 or 24 weeks resulted in SVR12 rates of 99% or greater,” Dr. Murray said.

Press conference moderator Frank Tacke, MD, of University Hospital Aachen in Germany, commented, “This study is a breakthrough for the management of children ages 6 to 11 years old with HCV, demonstrating that the new DAA regimen is highly efficacious and, more importantly, safe in this group of HCV-infected children.”

A Two-Year Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Of Bezafibrate for the Treatment of Primary Biliary Cholangitis in Patients With Inadequate Biochemical Response to Ursodeoxycholic Acid Therapy (BEZURSO)

• Christophe Corpechot, MD, Reference Center for Inflammatory Biliary Diseases, Paris, France

A comparison of placebo and bezafibrate for primary biliary cholangitis (PBC) patients with inadequate responses to ursodeoxycholic acid (UDCA) therapy showed both benefit and safety for the fibrate, according to results of the BEZURSO trial. PBC, a chronic autoimmune disease that affects mostly middle-aged women, can damage and eventually destroy bile ducts, leading to cirrhosis, liver failure, and cancer, Dr. Corpechot said.
in a late-breaking clinical trial session and at an EASL press conference. PBC may progress silently for years, with fatigue and pruritis as its emerging symptoms. While no curative therapies exist, a large proportion of patients respond to UDCA, which can slow bile duct destruction and disease progression and significantly improve liver function tests. More than 30% of patients, however, do not respond adequately to UDCA, leaving them at high risk for disease progression, reduced survival, and need for liver transplantation. “While reports on fibrates in PBC from small-sized, non-blinded, controlled studies have been encouraging, BEZURSO is the first large randomized trial of fibrates in patients with PBC who had responded inadequately to UDCA,” Dr. Corpechot said.

The primary objective of the BEZURSO trial was to assess the efficacy of bezafibrate (400 mg per day) as an adjunctive therapy to UDCA (13–15 mg/kg per day) for PBC in patients who did not respond adequately to UDCA alone. The primary endpoint was complete biochemical response as defined by normal levels of total bilirubin, alkaline phosphatase, amino-transferases, albumin, and prothrombin time at month 24. BEZURSO investigators randomized 100 patients with an inadequate biochemical response to UDCA (as defined by the Paris II criteria) to two years of UDCA 13–15 mg/kg per day in combination with either bezafibrate 400 mg per day or placebo. Normalization of liver function tests was the primary endpoint. Mean patient age was 53 years, and 95% were women.

At baseline, approximately 66% of patients reported pruritis, and about 54% were in an advanced disease stage. After 24 months, complete biochemical responses were reported in 30% of patients receiving bezafibrate and in 0% of patients receiving placebo (P < 0.0001). For the secondary endpoint of changes in biochemical tests, significant improvements in the bezafibrate group were found for total bilirubin (P < 0.0001), alkaline phosphatase (P < 0.0001), gamma-glutamyl transferase (P < 0.0001), aspartate transaminase (P < 0.05), alanine transaminase (P < 0.0001), albumin (P < 0.05), and cholesterol (P < 0.0001). “Itch” score reductions of –75% with bezafibrate were also significant (P < 0.01). Fibrosis markers of liver stiffness (+14% for placebo versus –10% for bezafibrate; P < 0.01) and enhanced liver fibrosis score (+3% for placebo versus –1% for bezafibrate; P < 0.05) also favored bezafibrate. Rates for end-stage liver complications were similar (4%) in both groups.

The rate for freedom from serious adverse events was 80% in the placebo group and 74% in the bezafibrate group (P = NS).

“In PBC patients with inadequate biochemical response to UDCA, adjunctive therapy with bezafibrate is safe, improves pruritus, normalizes biochemical prognostic markers, and prevents liver stiffness progression,” Dr. Corpechot concluded. “The findings support the use of bezafibrate in combination with UDCA as an effective second-line therapy for PBC.”

“This study could have an important impact on clinical practice,” commented Marco Marzioni, MD, Professor of Gastroenterology at University Hospital in Ancona, Italy, “as it shows that patients with PBC who do not respond adequately to current treatment with UDCA could obtain a notable benefit with additional bezafibrate therapy, a drug which is already used for the treatment of hypercholesterolemia.”

Nivolumab in Sorafenib-Experienced Patients With Advanced HCC With or Without Chronic Viral Hepatitis: The CheckMate 040 Study

• Bruno Sangro, MD, Clinica Universidad de Navarra, Pamplona, Spain, and Centro de Investigación Biomédica en Red, Madrid, Spain

Survival was increased and responses were sustainable when patients with advanced hepatocellular carcinoma (HCC) who had previously been treated with sorafenib were given nivolumab (Opdivo, Bristol-Myers Squibb). Responses were demonstrated, Dr. Sangro said at an EASL press conference, among patients who had been infected with either hepatitis C or hepatitis B virus (HCV or HBV). The findings emerged from an interim analysis of CheckMate 040, an open-label, phase 1/2, dose-escalation, and expansion trial including 262 HCC patients.

Dr. Sangro noted that HCC, the second leading cause of cancer-related death, develops primarily from cirrhosis, and most HCC patients are infected with HCV or HBV. Currently, the only systemic therapy for advanced HCC patients is the multikinase inhibitor sorafenib. The majority of sorafenib-treated patients, however, progress and have no further treatment options. In addition, if patients are intolerant of or have contraindications to sorafenib, there is no standard of care. Nivolumab, a fully human monoclonal antibody inhibitor of the programmed cell death-1 receptor, restores T-cell–mediated anti-tumor activity. It has already demonstrated increased survival time in several cancer types and is an important treatment option for some renal and hematological cancers, and for melanoma and non–small-cell lung cancer. Preliminary CheckMate 040 results suggested promise for nivolumab in HCC.

Patients included in CheckMate 040 were not eligible for surgery. In the dose-expansion portion, among the 145 patients who had been treated previously with sorafenib, 132 (91.0%) had progression of their cancer, and 12 (8.3%) were intolerant of the therapy. All were given intravenous nivolumab 3 mg/kg every two weeks until HCC progression or the development of intolerable side effects. The primary endpoint was objective response rate (ORR) by blinded, independent central review.

After a median follow-up of 12.9 months, ORR in the dose-expansion group (n = 214) was 16.8%. ORR had been similar (16.7%) during the dose-escalation phase among 48 patients. ORR in patients who were sorafenib-naïve (n = 69) was 21.7%. Median overall survival (OS) for the entire group was 16.7 months; for those with chronic HCV or HBV, median OS had not yet been reached. Twelve-month OS was 67.1% in HCV-infected patients (n = 30), 55.6% in HBV-infected patients (n = 43), and 59.7% in uninfected patients (n = 72). The disease control rate (complete response plus partial response plus stable disease) for all patients was 55.9%.

Dr. Sangro pointed out that objective responses occurred regardless of tumor cell programmed death ligand-1 (PD-L1) expression (both less than 1% or 1% or greater). ORR was higher, however, in patients with PD-L1 expression of 1% or greater.

Most responses (12 of 21; 57%) occurred within three months of treatment, and 71% (15 of 21) were ongoing, with median
duration of response not reached for the overall group or any subgroup.

The overall safety of nivolumab in patients with or without chronic viral hepatitis was similar to that observed in other tumor types, and there were no new safety signals. Elevations in liver enzymes (aspartate transaminase and alanine transaminase) were reversible with established algorithms.

“In sorafenib-experienced patients with or without chronic viral hepatitis, nivolumab demonstrated long-term survival and durable objective responses with extended follow-up that were consistent across etiologies,” Dr. Sangro said.

A phase 3 evaluation (CheckMate 459) of nivolumab in systemic treatment-naive patients with advanced HCC is ongoing.

SARAH: A Randomized, Controlled Trial Comparing Efficacy and Safety of Selective Internal Radiation Therapy (With Yttrium-90 Microspheres) and Sorafenib in Patients With Locally Advanced HCC

Valérie Vilgrain, MD, Hôpital Beaujon Service de Radiologie, Paris, France

“Patients with advanced or inoperable hepatocellular carcinoma [HCC] have a poor prognosis, often with underlying cirrhosis, and the treatment option currently available, sorafenib, has a high level of toxicity,” Dr. Vilgrain stated at an EASL press briefing presentation of SARAH trial results. She further noted that HCC, the second most common cause of cancer-related deaths worldwide, represents more than 90% of primary liver cancers. The multikinase inhibitor sorafenib is the only approved first-line systemic treatment, and there is currently no standard of care for sorafenib-intolerant patients or for those who have sorafenib contraindications.

Dr. Vilgrain’s SARAH study aimed to test the efficacy of selective internal radiation therapy (SIRT) with yttrium (Y)-90 microspheres in advanced HCC in a direct comparison with sorafenib, the standard of care. In the SHARP trial of sorafenib versus placebo in advanced HCC, median overall survival (OS) with sorafenib was 10.7 months versus 7.9 months for placebo. Large cohort studies have previously demonstrated SIRT’s efficacy. “We set out to compare the efficacy of this treatment versus the current standard of care,” Dr. Vilgrain said.

SARAH is a prospective, open-label, phase 3, multicenter, randomized, and controlled trial in patients with locally advanced and inoperable HCC who have failed two rounds of transarterial chemoembolization, the reference treatment for intermediate HCC. The primary endpoint is OS. Secondary endpoints include progression-free survival (PFS), incidence of intrahepatic and extrahepatic progression, and tumor response rate.

The SARAH trial enrolled 467 patients at 25 French sites, randomizing them 1:1 to sorafenib 800 mg per day or SIR-Spheres Y-90 resin microspheres (Sirtex). Ultimately, 174 patients received SIRT and 206 received sorafenib (26.6% did not receive SIRT, and 7.2% did not receive sorafenib per protocol). Mean age was approximately 65 years, about 90% of patients had cirrhosis, and approximately 90% were men. In the intent-to-treat analysis (n = 459) of median OS, the rates were 8.0 months for SIRT and 9.9 months for sorafenib (hazard ratio [HR], 1.15; 95% confidence interval [CI], 0.94–1.44; \( P = 0.18 \)). In the per-protocol analysis (n = 380), median OS was 9.9 months for both SIRT and sorafenib (HR, 0.99; 95% CI, 0.79–1.24; \( P = 0.92 \)). PFS was similar for both treatments in both the intent-to-treat analysis (4.1 months for SIRT versus 3.7 months for sorafenib; \( P = 0.76 \)) and per-protocol analysis (4.3 months for SIRT versus 3.7 months for sorafenib; \( P = 0.77 \)). An intent-to-treat analysis of radiological progression in the liver as the first site, however, revealed significantly lower incidence in the SIRT group than in the sorafenib group (\( P = 0.027 \)). In addition, the tumor response rate (using RECIST 1.1 criteria of complete response plus partial response) was higher for SIRT (19.0%) than for sorafenib (11.6%) (\( P = 0.042 \)). “These indicate a strong signal for local effects within the liver for Y-90 microspheres,” Dr. Vilgrain said.

Grade 3 or higher treatment-related adverse events were fewer with SIRT (n = 230) than with sorafenib (n = 411), with half of the median number of adverse events per person with SIRT than with sorafenib. Fatigue, weight loss, infection, hand-foot skin reaction, diarrhea, abdominal pain, and hypertension were all significantly lower with SIRT than with sorafenib. Quality of life, assessed using the Global Health Status scale of the European Organization for Research and Treatment of Cancer QLQ–C30 questionnaire, was significantly better with SIRT than with sorafenib. Expectancy, so quality of life is a priority,” Dr. Vilgrain concluded.

Two radiation-induced complications were reported in the SIRT group.

In response to press conference questions, Dr. Vilgrain noted that the shorter OS for sorafenib in the SARAH trial than in the SHARP trial may be attributed to more advanced disease in SARAH patients, particularly with 60% having vascular invasion, a major prognostic factor for adverse outcomes. In addition, a greater number of patients treated with SIRT than with sorafenib became eligible for curative treatments, such as liver resection, tumor ablation, or transplantation. Finally, she suggested that the roughly 50-patient reduction in the number of patients who ultimately got SIRT was due to the two- to three-week delay between the work-up and treatment. That process, which includes imaging to determine likely uptake of Y-90 microspheres, is being reduced to a single day in ongoing studies.

“While SIRT did not increase overall survival in this population, it offered a higher tumor response, better tolerance with less treatment-related adverse events, and a better quality of life over time. We think these issues are extremely important because these patients have severe disease with poor life expectancy, so quality of life is a priority,” Dr. Vilgrain concluded.