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Managing Cirrhosis: New Data on Liver Disease Complications

A Review of Selected Presentations from the 59th Annual Meeting of the American Association for the Study of Liver Diseases
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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists and hepatologists involved in the management of patients with cirrhotic liver disease.

Statement of Need/Program Overview:

The incidence rate of hepatocellular carcinoma (HCC) is the fifth highest among tumors worldwide and similar in size to the death rate. Hepatic cirrhosis has been recognized as the most important risk factor for the development of HCC. Treatment options for HCC continue to expand and improve. Techniques for radiofrequency ablation and transarterial chemoembolization have allowed for more successful treatment in the early stages of disease. For patients with later-stage disease, improvements in terms of survival time and time-to-tumor progression have been shown with the use of the oral targeted therapy sorafenib. Future research will investigate the use of all of these modalities in different combinations and at different timepoints to further optimize their efficacy.

The primary goals of hepatic encephalopathy (HE) treatment are to prevent episodic deterioration of cognitive function, provide salvage therapy to patients experiencing episodic deterioration, and produce improvements in patients with persistent or minimal HE. HE can be cured with liver transplantation, but not all patients are eligible for this procedure. The current standard treatment for HE in the United States is lactulose. It is often poorly tolerated by patients, which may affect compliance. Standard antibiotics for HE include neomycin, as well as rifaximin and metronidazole, neither of which have an official indication. However, experience with rifaximin is well-published, and it currently has FDA-designated orphan drug status for HE.

As new data are announced at scientific meetings, summaries and analysis by expert opinion leaders can assist clinicians in detecting the disease and making effective decisions with regard to therapeutic options. An abstract summary including important cirrhosis-related data from the 2008 AASLD meeting would provide an excellent educational resource for readers of *Gastroenterology & Hepatology*.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Outline challenges in the detection and treatment of all stages of hepatic encephalopathy.
2. Recall the latest data on the use of rifaximin as a treatment option.
3. Review the role of VEGF as a prognostic indicator in HCC.
4. Describe the efficacy and side effects of sorafenib in the treatment of HCC.

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Table of Contents

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New Data on Hepatic Encephalopathy

472 Does the Addition of Rifaximin to Lactulose Reduce the Severity of Hepatic Encephalopathy? A Single-Center Experience

PS Mantry, S Munsaf

Rifaximin is a nonabsorbed, gut-specific antibiotic, which does not enter the systemic circulation.[1] It is therefore designed to achieve high concentrations within the gastrointestinal tract. Recently, several studies have evaluated the activity of rifaximin to treat hepatic encephalopathy.[2] Generally, these studies have shown that rifaximin treatment is associated with fewer hospitalizations, shorter hospital stays, and improved tolerance compared with other hepatic encephalopathy treatments, including the disaccharide lactulose, a standard therapy.[3] Here, Mantry and Munsaf evaluate the efficacy of adding rifaximin to lactulose to treat hepatic encephalopathy.[4]

In this retrospective single-center study, 123 patients met the study inclusion criteria. All included patients had been evaluated for liver transplantation due to end-stage liver disease between January 2006 and March 2008. The investigators analyzed outcomes of hospitalizations due to hepatic encephalopathy during each treatment period. Of the total cohort, 58 patients received lactulose alone (20–120 g/day) for a mean duration of 24 months. The other 65 patients received adjunctive rifaximin (400–1,200 mg/day) for an average of 14 months, subsequent to lactulose monotherapy (20–120 g/day) for an average of 21 months. Among the lactulose alone and lactulose with adjunctive rifaximin treatment groups, the etiologies of cirrhosis included alcohol (38% and 37%, respectively), chronic hepatitis C infection (52% and 43%, respectively), and nonalcoholic steatohepatitis (17% and 22%, respectively). Mean duration of liver disease in the lactulose-alone arm was 22 years versus 20 years in the cohort receiving lactulose and adjunctive rifaximin.

Of the patients who received lactulose-alone therapy, 86% had a history of hepatic encephalopathy, and 33% had undergone an average of 1.2 prior hospitalizations due to hepatic encephalopathy. Of the patients who received lactulose followed by adjunctive rifaximin, all had a prior history of hepatic encephalopathy, and nearly half (46%) had an average of 2.6 prior hospitalizations for hepatic encephalopathy. Importantly, patients in the group receiving adjunctive rifaximin had an 87% reduced risk of hospitalization while receiving rifaximin compared to the time period during which they received only single-agent lactulose (17 versus 60 hospitalizations, respectively). This equated to a mean number of hospitalizations per patient of 0.26 versus 0.95, respectively, odds ratio: 0.13 (P<.001). Additionally, these patients had a 39% reduced risk of hospitalization compared with patients receiving lactulose alone (mean 0.40 hospitalizations per patient, odds ratio: 0.61 [P=.042]). Patients receiving adjunctive rifaximin also experienced a shorter mean duration of hospital stay compared with their prior single-agent lactulose therapy (1.1 versus 1.8 days per patient, respectively, P=.104) or those with lactulose treatment alone (1.1 versus 2.4 days per patient, respectively P=.04). Significantly, only 6% of patients receiving adjunctive rifaximin had more than one hospitalization, compared to 23% during their preceding single-agent lactulose therapy (P<.001). Comparatively, 5% who received lactulose alone had more than 1 hospitalization. The study reported that treatment, age, and MELD score were all independently predictive of hepatic encephalopathy hospitalization in multivariate analysis.

Mantry and Munsaf concluded that this retrospective study showed that adjunctive rifaximin during lactulose therapy reduced the number of hospitalizations and shortened the duration of hospitalization due to hepatic encephalopathy. The addition of rifaximin may reduce the significant morbidities associated with hepatic encephalopathy, resulting in therapeutic and economic benefit. Future prospective studies are needed to more deeply evaluate the potential therapeutic and pharmacoeconomic benefits of adjunctive rifaximin in this setting.

In a separate review of the same patient cohort, Mantry and Munsaf also compared rates of adverse events and spontaneous bacterial peritonitis (SBP) in patients who received lactulose versus those who received lactulose and subsequent adjunctive rifaximin.[5] They found evidence of SBP during treatment in 6 of 58 patients (10%) who received lactulose alone and in 8 of 65 patients (12%) during lactulose monotherapy preceding adjunctive rifaximin. During adjunctive rifaximin therapy, only 1 of 65 patients (2%) experienced SBP (P=0.051 and P=0.016,

respectively). Further, during adjunctive rifaximin therapy, versus preceding lactulose monotherapy, fewer patients developed AEs not considered serious (eg, cramping, bloating, abdominal pain, or excess diarrhea; 0 vs 56; $P<.001$) or discontinued treatment (1 vs 24; $P<.001$). The authors further concluded that combining rifaximin with lactulose treatment for HE substantially reduces the incidence of AEs and of SBP as compared with lactulose monotherapy.

1734 Analysis of the Effect of Rifaximin Plus Lactulose on Hospitalizations in Patients with End-Stage Liver Disease

PS Mantry, S Munsaf

Clinical studies have shown that the nonabsorbed antibiotic rifaximin is active in the treatment of hepatic encephalopathy. After patients began receiving rifaximin in addition to lactulose therapy, fewer hospitalizations, shorter hospital stays, and lower associated costs were reported.[6] Several additional studies that have randomized patients to receive either lactulose or rifaximin have shown that both treatments similarly improved measures of hepatic encephalopathy.[2] As its absorption into the systemic circulation is limited, rifaximin can reach high concentrations within the gastrointestinal tract.[7] Thus, this selective gut activity may be beneficial in other cirrhotic complications, including portal hypertension and spontaneous bacterial peritonitis. Here, Mantry and Munsaf performed a retrospective single-center study to evaluate the outcomes of non-hepatic encephalopathy-related hospitalizations in cirrhotic patients who had received rifaximin to treat hepatic encephalopathy.[8]

Medical charts for 65 patients with end-stage liver disease considered for liver transplantation between 2006 and 2008 were included in this retrospective cohort. All patients received single-agent lactulose (20–120 g/day for a mean duration of 21 months) followed by adjunctive rifaximin (400–1200 mg/day for a mean duration of 14 months) to treat hepatic encephalopathy. Each patient had a history of prior hepatic encephalopathy, and approximately half (46%) had an average of 2.6 prior hospitalizations for hepatic encephalopathy.

Patients experienced a lower mean number of hospitalizations during adjunctive rifaximin therapy compared to during the prior single-agent lactulose therapy (0.56 versus 0.80 hospitalizations per patient, respectively). Patients experienced a 16% reduced risk of hospitalization for non-hepatic encephalopathy conditions while receiving adjunctive rifaximin compared with single-agent lactulose (odds ratio: 0.84). Significantly fewer hospitalizations were recorded during the adjunctive rifaximin treatment period compared with the single-agent lactulose treatment period (5% vs 12% of patients had >1 hospitalization, $P=.006$). However, the mean duration of hospital stay for non-hepatic encephalopathy-related conditions was not significantly changed between the adjunctive rifaximin and single-agent lactulose treatment periods (2.5 days versus 2.0 days, respectively).

From these results, Mantry and Munsaf concluded that adjunctive rifaximin therapy may affect the rate of non-hepatic encephalopathy-related morbidities, and therefore reduce their associated rates of hospitalizations. As a result, adjunctive rifaximin may reduce overall hospitalization costs in cirrhotic patients. The authors suggest that future prospective studies are needed to confirm and further investigate the potential non-hepatic encephalopathy-related benefits of adjunctive rifaximin therapy.

1715 Inhibitory Control Test Detects Post-TIPS Psychometric Impairment

JA Bajaj, M Hafeezullah, JF Knox, RG Hoffman, K Saeian

Minimal hepatic encephalopathy is difficult to diagnose, largely due to the standard psychometric tests used in clinical diagnostic practice.[9,10] These tests require higher levels of psychological expertise and expense that is often not reimbursed by insurance companies. In contrast, the inhibitory control test is a relatively simple, less cumbersome test for minimal hepatic encephalopathy diagnosis. The inhibitory control test is a computerized test consisting of lures and targets, in which a high lure rate and low target rate represent poor performance.[11] The transvenous intrahepatic portosystemic shunting (TIPS) procedure is commonly used to treat complications associated with cirrhosis, and is a good model for validation of hepatic encephalopathy diagnostic tests.[12] In this setting, the diagnostic test is performed prior to and after a TIPS procedure, and the results are compared for improvement. Here, Bajaj and colleagues aimed to perform an external validation of the inhibitory control test using TIPS.[13]

A total of 10 cirrhotic patients underwent TIPS, and were evaluated with standard psychometric tests and the inhibitory control test prior to and within 30 days following TIPS. Patients underwent testing 26 ± 5 days prior to TIPS and 35 ± 3 days subsequent to TIPS. Patients under-

went TIPS for refractory ascites (n=6), hepatic hydrothorax (n=2), or chronic rectal variceal bleeding (n=2). An average reduction in hepatic portal venous pressure of 8.4 ± 2.6 mm Hg was observed. Prior to TIPS, 8 patients were diagnosed with minimal hepatic encephalopathy by standard psychometric tests and 7 by inhibitory control test. At the post-TIPS evaluation, 3 patients were noted to have developed overt hepatic encephalopathy and were therefore initiated on lactulose therapy. All 3 of these patients had minimal encephalopathy prior to TIPS, measured by both standard psychometric tests and inhibitory control test. Of the remaining 5 patients who had been diagnosed with minimal hepatic encephalopathy by standard psychometric tests prior to TIPS, this status remained unchanged. Significantly, there was an increase in lure response rate following TIPS.

Bajaj and colleagues concluded that performance on the inhibitory control test worsened after TIPS. The inhibitory control test was found to be equivalent with standard psychometric tests for diagnosing hepatic encephalopathy, thus validating its use for the detection of psychometric impairment in cirrhosis.

1716 Inhibitory Control Test is a Sensitive and Inexpensive Alternative for the Diagnosis of Minimal Hepatic Encephalopathy

JS Bajaj, M Hafeezullah, TA Hammeke, J Franco, RR Varma, RG Hoffman, K Saeian

As discussed above, the inhibitory control test is a computerized test of attention and response inhibition, which has been evaluated for its ability to diagnosis hepatic encephalopathy. In a previous study, the inhibitory control test was associated with a 90% sensitivity and specificity for the diagnosis of minimal hepatic encephalopathy in 50 non-alcoholic cirrhotic patients.[11] Here, Bajaj and colleagues aimed to further evaluate the reliability, validity, and cost-effectiveness of the inhibitory control test to diagnose minimal hepatic encephalopathy.[14]

For this analysis, the inhibitory control test was compared with the standard psychometric tests typically used to diagnose minimal hepatic encephalopathy. These included a number connection test, a digit symbol test, and a block design test. After administering twice to establish test/retest reliability, minimal hepatic encephalopathy was diagnosed if any of the standard psychometric test results were impaired over 2 standard deviations beyond control performance. To determine cost-effectiveness, the time used by a medical assistant to deliver the inhibitory control test was compared with the time used by a psychologist to administer the standard psychometric tests. A total of 136 cirrhotic patients were evaluated, of whom nearly half (n=72) were male and the median age was 51 years. A total of 87 patients were positive for minimal hepatic encephalopathy prior to the study. Cirrhotic patients were compared to age- and education-matched controls.

No significant differences were noted in either standard psychometric test performance or inhibitory control test performance among patients whose cirrhosis etiology was either chronic hepatitis C or alcohol. The inhibitory control test was associated with an 88% sensitivity rate and 77% rate of specificity for the diagnosis of minimal hepatic encephalopathy. Patients who had a diagnosis of minimal hepatic encephalopathy had a significantly higher rate of lures (11 versus 4, P=.0001) and lower rate of targets (92% versus 97%, P=.0001), compared with patients not diagnosed with minimal hepatic encephalopathy. The test/retest reliability for the inhibitory control test was high, with a score of r=0.90 (P=.0001) for the two administrations. Both the inhibitory control test and the standard psychometric tests equivalently predicted overt hepatic encephalopathy in 21% of cases. Compared with administration of standard psychometric tests, delivery of the inhibitory control test was inexpensive ($348 versus $41, respectively, for private insurance billing).

The authors concluded that the inhibitory control test was a reliable, sensitive, and valid test which could effectively be used to diagnose minimal hepatic encephalopathy. Additionally, it is inexpensive relative to the standard psychometric tests, and therefore may be an important tool for identifying this difficult-to-diagnose cirrhotic complication.

1731 Effect of Enforced Sleep Deprivation on Minimal Hepatic Encephalopathy

JS Bajaj, M Hafeezullah, R Franco, K Saeian

Sleep disturbances are a noted symptom of cirrhosis, either in the presence or absence of minimal hepatic encephalopathy. In fact, nearly half of cirrhotic patients in one survey complained of unsatisfactory sleep.[15] In a separate case-control study, patients with cirrhosis experienced significantly more daytime sleepiness, sleeping badly at night, and difficulty falling asleep.[16] This sleep disturbance may be associated with psychometric impairment, either together with or separate from the minimal

hepatic encephalopathy. However, a good model for sleep deprivation in cirrhosis is not established, as it is unclear if sleep deprivation of health controls can provide a model for minimal hepatic encephalopathy, or if sleep deprivation in cirrhotic patients with minimal hepatic encephalopathy leads to overt hepatic encephalopathy. Here, Bajaj and colleagues sought to evaluate psychometric function before and after sleep deprivation in cirrhotic patients with minimal hepatic encephalopathy.[17]

Several tests were used to evaluate patients prior to sleep deprivation. These included both standard psychometric tests such as number connection tests, block design, and digit symbol, as well as inhibitory control tests. Minimal hepatic encephalopathy was diagnosed if any two tests were impaired. Further, patient sleep deprivation at baseline was established using the Epworth Sleepiness Scale and the Pittsburgh Sleep Quality Index. A total of 2 weeks following the baseline examinations, all subjects (cirrhotic patients and matched controls) were sleep deprived for 24 hours under supervision in a sleep laboratory. The morning following sleep deprivation, all subjects were evaluated for overt hepatic encephalopathy by re-administration of the same battery of tests.

A total of 5 male patients (median age 50 ± 8 years) with minimal hepatic encephalopathy were compared with 5 age- and sex-matched controls. Significantly, cirrhotic patients with minimal hepatic encephalopathy were more psychometrically impaired than controls at baseline. At baseline, no significant differences existed in sleep deprivation among either cirrhotic patients or controls. Importantly, none of the cirrhotic patients developed overt hepatic encephalopathy following sleep deprivation. Further, no change in psychometric performance was observed following sleep deprivation in either group. No control participant reached the threshold for diagnosis of minimal hepatic encephalopathy after sleep deprivation.

The authors concluded that sleep deprivation was not a good model for minimal hepatic encephalopathy, as it did not consistently impair psychometric performance in the control subjects, nor did it significantly worsen psychometric tests or induce overt hepatic encephalopathy in cirrhotic patients with minimal hepatic encephalopathy.

References

1. Bass NM. Review article: the current pharmacological therapies for hepatic encephalopathy. *Aliment Pharmacol Ther*. 2007;25(Suppl 1):23-31.
2. Lawrence KR, Klee JA. Rifaximin for the treatment of hepatic encephalopathy. *Pharmacotherapy.* 2008;28:1019-1032.
3. Maclayton DO, Eaton-Maxwell A. Rifaximin for Treatment of Hepatic Encephalopathy (January). *Ann Pharmacother*. 2008.
4. Mantry P, Munsaf S. Does the addition of rifaximin to lactulose reduce the severity of hepatic encephalopathy? A single-center experience. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 472.
5. Mantry PS, Munsaf S. Comparison of tolerability of adjunctive rifaximin treatment versus lactulose monotherapy for hepatic encephalopathy. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 473.
6. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci.* 2007;52:737-741.
7. Gerard L, Garey KW, DuPont HL. Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. *Expert Rev Anti Infect Ther.* 2005;3:201-211.
8. Mantry P, Munsaf S. Analysis of the effect of rifaximin plus lactulose on hospitalizations in patients with end-stage liver disease. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1734.
9. Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. *J Hepatol.* 2001;34:768-773.
10. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35:716-721.
11. Bajaj JS, Saeian K, Verber MD, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. *Am J Gastroenterol.* 2007;102:754-760.
12. Colombato L. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. *J Clin Gastroenterol.* 2007;41(Suppl 3): S344-S51.
13. Bajaj J, Hafeezullah M, Knox J, Hoffman R, Saeian K. Inhibitory control test detects post-TIPS psychometric impairment. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1715.
14. Bajaj J, Hafeezullah M, Hammeke T, et al. Inhibitory control test is a sensitive and inexpensive alternative for the diagnosis of minimal hepatic encephalopathy. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008: Abstract 1716.
15. Cordoba J, Cabrera J, Lataif L, Penev P, Zee P, Blei AT. High prevalence of sleep disturbance in cirrhosis. *Hepatology*. 1998;27:339-345.
16. Mostacci B, Ferlisi M, Baldi Antognini A, et al. Sleep disturbance and daytime sleepiness in patients with cirrhosis: a case control study. *Neurol Sci*. 2008;29: 237-240.
17. Bajaj J, Hafeezullah M, Franco R, Saeian K. Effect of enforced sleep deprivation on minimal hepatic encephalopathy. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1731.

Commentary

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Despite recent advances in the treatment of viral hepatitis, the prevalence of hepatic cirrhosis continues to rise in the United States through a variety of epidemiologic factors, including the maturation of the hepatitis C epidemic, rising rates of obesity and fatty liver disease, and the ongoing incidence of alcoholic cirrhosis. With the management of the growing pool of cirrhotic patients comes a need for greater awareness of hepatic encephalopathy as a complication of this condition. Data presented at the recent AASLD meeting provide new insights into the treatment and detection of this syndrome.

The study by Mantry and Munsaf confirms findings from previous publications, showing that rifaximin is more effective than lactulose in preventing hepatic encephalopathy-related hospitalizations and shortening lengths of stay. The overall benefit of rifaximin therapy will decrease patient morbidity and mortality. In conclusion, rifaximin as seen in previous reports, is reconfirmed by Mantry and Munsaf to be the recommended therapy for patients suffering from hepatic encephalopathy, particularly with regard to the important treatment goal of avoiding hospitalization.

In a second study, the same group reveals a decrease in hepatic encephalopathy-related hospitalizations and a decrease in lengths of stays, when lactulose-treated patients receive adjunctive rifaximin therapy. The conclusions of both of these studies provide valuable information to both patients and caregivers in the effort to avert potential complications associated with hepatic encephalopathy. They also allow for cost analysis showing that rifaximin therapy provides savings in hepatic encephalopathy management, when considering the prevention of hospitalizations and shortening of hospital courses. Further, the initial cost advantages offered by the use of lactulose can be lost when patients fail to control their hepatic encephalopathy with drug adjustments, resulting in reduced quality of life and more frequent hospitalizations.

Optimization of resources, including time in the clinic, is an area of concern in the growing population of cirrhotic patients. Bajaj and associates present data on the inhibitory control test, a computerized test of attention and response inhibition and a potential alternative to standard psychometric evaluations of hepatic encephalopathy. Their evaluation demonstrated the inhibitory control test to be reliable, sensitive, and valid. Present methods for determining hepatic encephalopathy can be cumbersome and consume considerable time, prolonging already lengthy clinical consultations related to cirrhosis management. These findings offer caregivers a quicker, validated alternative for screening and surveillance for non-overt hepatic encephalopathy manifestations. Future studies will further evaluate and validate this method in the hopes of establishing the inhibitory control test as the method of choice in identifying patients with minimal hepatic encephalopathy.

The same group conducted another study to examine a possible association between sleep deprivation and minimal hepatic encephalopathy. Sleep deprivation is a common complication that affects a large percentage of cirrhotic patients. As a symptom, it can compound overall morbidity and is often difficult to distinguish from the effects of minimal hepatic encephalopathy. Bajaj and associates concluded that sleep deprivation did not worsen or propagate hepatic encephalopathy as none of the 5 patients in the trial reached the study threshold for minimal hepatic encephalopathy following the development of sleep deprivation. Overall, the work presented at the 2008 AASLD provided confirmation and showed progress in overcoming the diagnostic and management challenges presented by cirrhosis. Further investigation is warranted into the overall clinical and economic effectiveness of rifaximin. Additionally, the reports above show the importance early diagnosis of hepatic encephalopathy in the cirrhotic patient.

Suggested Reading

Bell BP, Manos MM, Zaman A, Terrault N, Thomas A, et al. The epidemiology of newly diagnosed chronic liver disease in gastroenterology practices in the United States: results from population-based surveillance. *Am J Gastroenterol*. 2008;103:2727-2736.

Bass NM. Review article: the current pharmacological therapies for hepatic encephalopathy. *Aliment Pharmacol Ther*. 2007;25(Suppl 1):23-31.

Qadri AM, Ogunwale BO, Mullen KD. Can we ignore minimal hepatic encephalopathy any longer? *Hepatology*. 2007;45:547-548.

Neff GW, Kemmer N, Zacharias VC, Kaiser T, Duncan C, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. *Transplant Proc*. 2006;38:3552-3555.

New Data on Hepatocellular Carcinoma

1450 Vascular Endothelial Growth Factor (VEGF) as a Predictor of Survival in Hepatocellular Carcinoma: Systemic Review and Meta-Analysis

SJ Schoenleber, DM Kurtz, JA Talwalkar, LR Roberts, GJ Gores

Hepatocellular carcinomas (HCC), like many other solid tumors, are notable for their highly vascularized structure.[1] This allows adequate delivery of nutrients and oxygen to the tumor cells to ensure their survival and prognosis. Not surprisingly, these tumors express a high level of the vascular endothelial growth factor (VEGF), a pro-angiogenic ligand.[2] VEGF upregulation is linked with the angiogenesis and vascular invasion of HCC.[3] Previously, studies have evaluated the use of tissue-based and serum-based VEGF levels as a potential predictive marker for HCC.[4,5] However, the true predictive ability of VEGF still remains unclear. Here, Schoenleber and colleagues performed a systematic review and meta-analysis of multiple studies which have evaluated the predictive use of VEGF to indicate survival in patients with HCC.[6]

The authors included studies which compared either serum or tissue VEGF levels with either overall survival or disease-free survival in HCC patients. Two independent reviewers performed data extraction, and a meta-analysis was used to combine the relative risk calculated in individual studies. A total of 8 serum VEGF level studies were included, 7 of which evaluated overall survival (n=579) and 5 of which analyzed disease-free survival (n=439). A total of 8 tissue VEGF level studies were also included, of which 4 evaluated overall survival (n=251) and 6 evaluated disease-free survival (n=413). A quality analysis, using the Ottawa Newcastle Quality Assessment Scale, showed that the quality of the serum VEGF level studies was slightly higher compared to tissue VEGF level studies, although this did not reach statistical significance.

This study found that overall survival was significantly worse in patients with high serum VEGF levels (relative risk: 2.33, 95% confidence interval (CI): 1.74–3.14, $P<.001$). Similarly, disease-free survival was also significantly worse in these patients (relative risk: 2.36, 95% CI: 1.76–3.16, $P<.001$). High VEGF tissue levels were also predictive of poor overall survival (relative risk: 2.15, 95% CI: 1.26–3.68, $P=.005$) and disease-free survival (relative risk: 1.61, 95% CI: 1.01–2.56, $P=.047$). The investigators reported a high degree of inter-study consistency among the serum and the tissue VEGF studies.

From this meta-analysis, Schoenleber and colleagues concluded that both serum and tissue VEGF levels were predictive of overall survival and disease-free survival in patients with HCC. However, they acknowledged that because of its applicability to quantitation, its lack of reliance on subjective pathologic interpretation, and higher evidence quality, serum VEGF levels may be superior to tissue VEGF levels for predictive analyses.

1453 Pilot Study of Sirolimus in Cirrhotic Patients with Advanced Hepatocellular Carcinoma

T Decaens, A Luciani, E Itti, A Hulin, M Hurtova, A Laurent, D Cherqui, A Mallat, C Duvoux

Recently, signaling through the mammalian target of rapamycin (mTOR) protein was shown to be a critical step in the pathogenesis of HCC.[7] Small molecule drugs targeting mTOR have shown some encouraging antitumor activity in experimental and preclinical models of HCC.[8-10] Here, Decaens and colleagues reported a pilot study of the safety and efficacy of sirolimus in patients with advanced HCC.[11]

A total of 14 patients with advanced HCC were included. The median patient age was 59 years (range: 32–77 years). Patients had a performance score of 0 or 1, and a median alpha-fetoprotein (AFP) level of 2,491 ng/mL (range: 4.2–189,060 ng/mL). All patients were naïve to systemic therapy and recruited between February and June of 2007. The HCC diagnosis was confirmed according to EASL criteria, and patients with renal failure and non-measurable disease were excluded from the study. Of the 14 total patients, 13 exhibited tumoral portal thrombosis. Patients were administered oral sirolimus (30 mg once weekly). The primary study endpoints were efficacy and safety, measured by the objective response rate estimated by monthly magnetic resonance imaging (MRI).

During the study, the reported drug-related adverse events included mucositis (35%), asthenia (28%), and

skin toxicity (28%). Of these, only one grade 3 event was reported (mucositis), and no grade 4 toxicities were observed. Patients experienced no liver-related toxicities, and no grade 3 or 4 hematologic toxicities. The study reported that among 11 of the 14 patients who were evaluable for efficacy analysis, 4 (36%) patients exhibited an objective response. One of these was a complete response.

The investigators concluded that the results of this pilot study suggest that sirolimus is active and has an acceptable safety profile in patients with cirrhosis-related HCC. The authors suggest that larger studies in HCC patients with early-stage cirrhosis are required in order to fully determine the impact of sirolimus on patient survival and any potential adverse effects.

1472 Significance and Management of Adverse Events Associated with Systemic Therapy with Sorafenib in Patients with Advanced Hepatocellular Carcinoma

P Hilgard, JM Ertle, V Penndorf, S Haag, G Gerken

Sorafenib is a multi-targeted tyrosine kinase inhibitor that has activity against several kinases including Raf, the VEGF receptor, and the platelet-derived growth factor (PDGF) receptor.[12] Sorafenib recently gained approval in both the United States and Europe as the first active systemic therapy for HCC.[13-15] Several studies have evaluated sorafenib in this setting.[16,17] In one study in unresectable HCC, sorafenib was associated with a significant survival advantage compared with placebo.[16] As is the case with many multi-targeted anti-tumor drugs, sorafenib is associated with a variety of adverse events which have not been fully defined in the setting of clinical practice.[18] These adverse events can potentially compromise the patient dosing schedule, and thus potential survival and patient quality of life. In this study, Hilgard and colleagues sought to prospectively determine the incidence and seriousness of sorafenib-associated adverse events in patients treated for HCC under non-selective clinical conditions.[19] Additionally, the authors aimed to define effective and optimal management strategies to treat the most common of these adverse events.

A total of 61 patients with advanced HCC were identified between February 2007 and May 2008. No patients were eligible for any locoregional treatment, and had either Child stage A (n=39) or Child stage B (n=22) liver function. Patients received a starting dose of 400 mg twice daily sorafenib. The investigators prospectively identified, evaluated, and graded adverse events during the course of the study.

A total of 86% of patients experienced an adverse event. The most common of these was diarrhea, which developed in 27 patients; the majority of these cases (82%) were categorized as grade 1. Grade 1 diarrhea was generally treated by oral supplementation with the Nissle strain of *Escherichia coli* (100 mg daily), and patients with persistent grade 1 or 2 diarrhea further received the anti-diarrheal agent loperamide (up to 8 mg daily). Only 1 patient required a dose reduction of sorafenib due to diarrhea. Hand-foot-skin reaction was recorded in 20 patients, of whom 17%, 9%, and 7% were grade 1, 2, and 3, respectively. The authors identified this as the single adverse event which required the most numbers of sorafenib dose reductions (to 200 mg twice daily after a 10 day discontinuation of sorafenib). Grade 1 hand-foot-skin reaction was treated locally by panthenol and urea ointment, whereas patients with grade 2 and 3 reactions also received local hempseed-oil ointment therapy. All other adverse events that were recorded were treated symptomatically, and improved in 76% of cases. The investigators reported no correlation between either the frequency or development of adverse events and impaired liver function, vessel invasion, or extrahepatic metastases.

The authors concluded that although adverse events following sorafenib treatment occurred frequently, most could be effectively treated without requiring dose reductions. Thus, sorafenib should be considered a safe treatment for patients with HCC.

1476 Applicability and Safety of Sorafenib for the Treatment of Advanced Hepatocellular Carcinoma in the Conventional Clinical Practice

ME Reig, A Forner, J Rimola, C Ayuso,
C Rodriquez de Lope, JM Llovet, J Bruix

Although sorafenib is accepted as front-line therapy for the treatment of HCC, its safety and efficacy have not been determined outside the confines of a clinical trial. Therefore, Reig and colleagues aimed to evaluate the efficacy and safety of sorafenib in patients with HCC not enrolled in a clinical trial.[20]

A total of 85 patients were prospectively identified between October 2007 and May 2008. Of these, 45 had contraindications to therapy (including uncontrolled arterial hypertension and symptomatic arterial disease), and

therefore only 40 began sorafenib therapy. All patients were identified within a referral liver cancer center. The median patient age was 66 years (range: 49–76 years), and 87% were males. All patients had underlying cirrhosis, and 58% were hepatitis C-positive.

Patients experienced a mean treatment duration of 84.5 days (range: 16–222 days). Dose modification due to adverse events was required in 62% of patients (n=25), at a median follow-up time of 26 days (range: 3–110 days). The median time of these adverse events occurred at 7 days (range: 1–91 days), and occurred at an average rate of 5 adverse events per patient (range: 1–12 events per patient). Of the 25 patients requiring dose modification, the sorafenib dosage was cut in half in 12 patients, whereas the remaining 13 patients underwent treatment discontinuation. Sorafenib therapy was reinitiated in all but 5 patients. The main causes of dose modification in this study were grade 2 or 3 hand-foot-skin reaction (17.5% and 5%, respectively), performance status impairment (15%), arterial hypertension (8%), and diarrhea (3%).

Reig and colleagues concluded that most adverse events occurring due to sorafenib therapy are minor. Of the adverse events requiring symptomatic control, proper therapy can allow continued therapy at the optimal dosage. Patients should be carefully followed during the first 3 weeks of therapy to establish, detect, and manage any adverse events. In order to avoid treatment cancellation, patients and health care teams should be properly educated to allow early detection and avoidance of treatment interruption.

References

1. Sugimachi K, Tanaka S, Terashi T, Taguchi K, Rikimaru T. The mechanisms of angiogenesis in hepatocellular carcinoma: angiogenic switch during tumor progression. *Surgery*. 2002;131:S135-41.
2. Yang ZF, Poon RT. Vascular changes in hepatocellular carcinoma. *Anat Rec (Hoboken)*. 2008;291:721-734.
3. Zhao ZC, Zheng SS, Wan YL, Jia CK, Xie HY. The molecular mechanism underlying angiogenesis in hepatocellular carcinoma: the imbalance activation of signaling pathways. *Hepatobiliary Pancreat Dis Int*. 2003;2:529-36.
4. Guo RP, Zhong C, Shi M, et al. Clinical value of apoptosis and angiogenesis factors in estimating the prognosis of hepatocellular carcinoma. *J Cancer Res Clin Oncol.* 2006;132:547-55.
5. Qin LX, Tang ZY. The prognostic molecular markers in hepatocellular carcinoma. *World J Gastroenterol*. 2002;8:385-92.
6. Schoenleber S, Kurtz D, Talwalkar J, Roberts L, Gores G. Vascular endothelial growth factor (VEGF) as a predictor of survival in hepatocellular carcinoma: systemic review and meta-analysis. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1450.
7. Villanueva A, Chiang DY, Newell P, et al. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology.* 2008;135:1972-83, 83 e1-11.
8. Tam KH, Yang ZF, Lau CK, Lam CT, Pang RW, Poon RT. Inhibition of mTOR enhances chemosensitivity in hepatocellular carcinoma. *Cancer Lett.* 2009;273:201-209.
9. Piguet AC, Semela D, Keogh A, et al. Inhibition of mTOR in combination with doxorubicin in an experimental model of hepatocellular carcinoma. *J Hepatol.* 2008;49:78-87.
10. Nocera A, Andorno E, Tagliamacco A, et al. Sirolimus therapy in liver transplant patients: an initial experience at a single center. *Transplant Proc.* 2008;40:1950-2.
11. Decaens T, Luciani A, Itti E, et al. Pilot study of sirolimus in cirrhotic patients with advanced hepatocellular carcinoma. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1453.
12. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther.* 2008;7:3129-40.
13. Pang RW, Poon RT. From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. *Oncology*. 2007;72 Suppl 1:30-44.
14. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology.* 2008;134:1752-63.
15. Zhu AX. Development of sorafenib and other molecularly targeted agents in hepatocellular carcinoma. *Cancer.* 2008;112:250-259.
16. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25-34.
17. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390.
18. Bhojani N, Jeldres C, Patard JJ, et al. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol.* 2008;53:917-930.
19. Hilgard P, Ertle J, Penndorf V, Haag S, Gerken G. Significance and management of adverse events associated with systemic therapy with sorafenib in patients with advanced hepatocellular carcinoma. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008:Abstract 1472.
20. Reig M, Forner A, Rimola J, et al. Applicability and safety of sorafenib for the treatment of advanced hepatocellular carcinoma in the conventional clinical practice. Presentation at the 59th Annual Meeting of the American Association for the Study of Liver Diseases; San Francisco, CA;October 31-November 4, 2008: Abstract 1476.

Commentary

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Investigations of HCC pathophysiology and treatment as presented at the recent AASLD meeting represent an ongoing evolution in our understanding of this tumor. With the ongoing expansion of medical therapy options for solid-tumor malignancies, it is important to understand strategies for optimization as well as the limitations of the available agents for treatment.

Recent interest in the role of VEGF as both a prognostic indicator and therapeutic target has been spurred by the successful use of sorafenib to treat HCC. Sorafenib is an inhibitor of the VEGF receptor, as are several other agents currently under investigation for the same indication. The promise of these agents in providing more effective treatment indicates a need for better understanding of VEGF as it relates to tumor growth, disease progression, and likelihood of metastasis.

The role of VEGF in HCC progression has been studied sporadically in the past. One study from Japan, which drew little attention at the time but seems more pertinent today, noted that patients who were treated for HCC before 1987 and those treated after that year had markedly different survival outcomes. At the time, the authors postulated that better outcomes were attributable to advances in cirrhosis management.

However, it was also noted that the later patients, who lived longer, also had a much greater chance of developing bone metastases, which indicate vascular progression of the disease. Vascular progression and metastasis can be correlated with an increased VEGF level, a finding that the authors did note in these patients. As a secondary conclusion, the authors noted that as patients live longer, VEGF will become elevated and cause more metastatic disease.

Thus, Gores and colleagues provide potentially useful data on VEGF measures as a predictive marker for HCC progression and survival. Their comparison of serum versus tissue levels of VEGF further refines our understanding of systemic manifestation. Their findings clearly indicate that overall survival can be correlated to both serum and tissue levels of VEGF but that serum measurements should be the focus of future research, given their better facility for objective, quantitative measure.

Whether VEGF levels will ever be found to be relevant as a predictive marker for current medical therapies remains to be seen. As mentioned above, current oral therapies are designed specifically to target the VEGF receptor and suppress its response to VEGF. Thus the measure of VEGF may have no bearing on treatment outcome when its receptor is being actively neutralized with therapy.

Regardless, as steps are taken to further optimize therapy through individualized drug regimens, measure of VEGF may remain a valuable prognostic tool. Gores and colleagues have laid valuable groundwork in the future development of protocols to consistently measure this marker.

The study by Decaens and associates of sirolimus for the treatment of HCC is interesting but limited due to the size of the patient population. Although the results are encouraging, a randomized phase II trial remains to be performed. The authors rightfully recommend further study of patients in earlier stages of cirrhosis. A larger study restricted to only Childs-Pugh A patients would give clearer results in terms of the potential efficacy of this agent.

Another consideration will be the challenge of recruiting patients with advanced HCC who are naive to medical therapy. Future studies will likely need to be performed in the setting of failure of sorafenib as this agent has assumed the role of standard first-line therapy for advanced disease.

Hilgard and colleagues provide some surprising outcomes on the side effects of sorafenib but in an extremely limited number of patients. With 61 subjects, their cohort is only about 1/10 the size of the pivotal Phase III SHARP trial and thus it is difficult to draw meaningful conclusions from their data. Their finding of grade 1 diarrhea in 82% of patients is particularly surprising as other experience has shown much lower rates. Hand-foot reactions occur-

ring in 20 patients, or about one third, seems to concur more closely with clinical experience of the drug.

With regard to treatment for these side effects, there are very well delineated guidelines in the dermatologic literature, authored by Lacouture, regarding the hand-foot syndrome, which can provide additional, definitive information.

More likely than not, if patients experience a grade 2 or 3 toxicity, they will require dose reduction. I would caution against assuming that administration of sorafenib can be undertaken without close monitoring for side effects and the possible need for adjustment of the dose. Sorafenib is a relatively safe agent. However, there are well-documented toxicities that might require symptom intervention as well as dose reductions when deemed necessary.

Bruix, Llovet, and associates examine similar issues in an even smaller cohort but their findings seem to contradict some of the conclusions of the Decaens cohort. Of their total population of 44 patients receiving sorafenib therapy, 62% actually required a dose modification. Their findings and conclusions clearly raise the issue of concerns with regard to toxicity and their data more closely match the findings reported in the SHARP trial. Importantly, they reinforce the message that patients should be carefully monitored, particularly in the first 3 weeks, and dose reductions need to be considered if they are symptomatic. A larger study will be necessary to fully address toxicity concerns regarding sorafenib.

Suggested Reading

Abou-Alfa GK, Venook AP. The impact of new data in the treatment of advanced hepatocellular carcinoma. *Curr Oncol Rep*. 2008;10:199-205.

Abou-Alfa GK. Hepatocellular carcinoma: molecular biology and therapy. *Semin Oncol*. 2006;33(6 Suppl 11):S79-S83.

Iguchi H, Uchimura K, Yokota M, Sumii T, Funakoshi A. Increased incidence of bone metastases and its management in hepatocellular carcinoma (HCC). *Proc Am Soc Clin Oncol*. 2003:22;abstr. 1250.

Lacouture ME, Wu S, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist*. 2008;13:1001-1011.

Notes

Managing Cirrhosis: New Data on Liver Disease Complications

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following statements about rifaximin is TRUE?
   a. Several studies have shown rifaximin is effective for the treatment of hepatorenal syndrome.
   b. Rifaximin is not systemically absorbed and is therefore able to achieve high concentrations within the gastrointestinal tract.
   c. Rifaximin is an antifungal agent which has been shown to be active in the treatment of hepatic encephalopathy.
   d. Rifaximin is nearly completely systemically absorbed and therefore reaches rapid high blood plasma concentrations.

2. In a retrospective single-center study by Mantry and Munsaf, patients receiving lactulose with adjunctive rifaximin had an _____ reduced risk of hospitalization compared to the time period during which they received lactulose alone.
   a. 23%
   b. 39%
   c. 86%
   d. 87%

3. In another retrospective single-center study by Mantry and Munsaf, treatment with lactulose plus adjunctive rifaximin resulted in a _____ reduced risk of hospitalization for non-hepatic encephalopathy conditions.
   a. 16%
   b. 33%
   c. 64%
   d. 84%

4. According to a study by Bajaj and colleagues in which the investigators performed an external validation of the inhibitory control test using TIPS, which of the following statements is TRUE?
   a. Patient performance on the inhibitory control test improved after undergoing TIPS.
   b. Patient performance on the inhibitory control test worsened after undergoing TIPS.
   c. Patient performance on the inhibitory control test remained unchanged after undergoing TIPS.
   d. The inhibitory control test was superior to the standard psychometric tests for diagnosing hepatic encephalopathy.

5. In a second study by Bajaj and colleagues, what was the rate of sensitivity for the diagnosis of minimal hepatic encephalopathy that the investigators attributed to the inhibitory control test?
   a. 44%
   b. 66%
   c. 77%
   d. 88%

6. According to a systematic review and meta-analysis of the predictive use of VEGF in HCC patients by Schoenleber and colleagues, which of the following is FALSE?
   a. High serum VEGF levels were significantly predictive of a poor overall survival.
   b. High serum VEGF levels were significantly predictive of a poor disease-free survival.
   c. Low VEGF tissue levels were significantly predictive of a poor overall survival.
   d. High VEGF tissue levels were significantly predictive of a poor overall survival.

7. In a pilot study by Decaens and colleagues, what proportion of HCC patients experienced an objective response to sirolimus?
   a. 28%
   b. 32%
   c. 36%
   d. 45%

8. According to Decaens and colleagues, what percentage of patients developed skin toxicities as as result of sirolimus administration?
   a. 17%
   b. 22%
   c. 28%
   d. 30%

9. In a study by Hilgard and colleagues, what was the most frequently experienced adverse event associated with sorafenib systemic therapy?
   a. Asthenia
   b. Diarrhea
   c. Hand-foot skin reaction
   d. Mucositis

10. A report by Reig and colleagues found which of the following statements to be TRUE?
    a. Most adverse events which occurred due to sorafenib therapy are serious in nature.
    b. The median time to adverse events was 14 days.
    c. Adverse events required dose modification in 62% of patients.
    d. Diarrhea was the most frequent cause of dose modification in these HCC patients.

Evaluation Form

Managing Cirrhosis: New Data on Liver Disease Complications

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Outline challenges in the detection and treatment of all stages of hepatic encephalopathy.	1	2	3	4	5
2. Recall the latest data on the use of rifaximin as a treatment option.	1	2	3	4	5
3. Review the role of VEGF as a prognostic indicator in HCC.	1	2	3	4	5
4. Describe the efficacy and side effects of sorafenib in the treatment of HCC.	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity. _____

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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