was also comparable in the 1- and 2-week groups (8.7 vs. 8.2).

Overall, our study demonstrated that when performing variceal ligation for the prevention of esophageal variceal bleeding, 1-week, compared to 2-week, intervals led to more-rapid eradication of varices without an increase in complications or an improvement in rebleeding. Until larger studies provide more information, we believe that the available evidence allows a range of choices regarding the interval for endoscopic ligation. Physicians and patients can use our results along with other available data to make individualized decisions, taking into account their preferences as well as local logistics and resources.

Sarah Sheibani, M.D.[1]
Loren Laine, M.D.[2]
[1]Keck School of Medicine
University of Southern California
Los Angeles, CA
[2]Yale School of Medicine
New Haven, CT and
VA Connecticut Healthcare System
West Haven, CT

REFERENCES

1) Sheibani S, Khemichian S, Kim JJ, Hou L, Yan AW, Buxbaum J, et al. Randomized trial of 1-week verus 2-week intervals for endoscopic ligation in the treatment of patients with esophageal variceal bleeding. HEPATOLOGY 2016;64:549-555.
2) Kumar S, Asrani SK, Kamath PS. Epidemiology, diagnosis and early patient management of esophagogastric hemorrhage. Gastroenterol Clin North Am 2014;43:765-782.
3) Wang HM, Lo GH, Chen WC, Chan HH, Tsai WL Yu HC, et al. Randomized controlled trial of monthly versus biweekly endoscopic variceal ligation for the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol 2014;29:1229-1236.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.28902

Potential conflict of interest: Nothing to report.

Nonalcoholic Fatty Liver Disease: Biomarkers Support Decisions Around Pharmacological Intervention

TO THE EDITOR:

We read with great interest the article of Ajmera et al.[1] reporting on the relationship between biomarkers and the histological disease spectrum of nonalcoholic fatty liver disease (NAFLD) in a large population of well-characterized patients from the Nonalcoholic Steatohepatitis Clinical Research Network. The researchers found a significant association between circulating levels of total plasminogen activator inhibitor 1 (tPAI1) and the presence of nonalcoholic steatohepatitis, which was independent of clinical confounding factors.[1] The clinical value of this result should be highlighted, also having important implications for tailoring pharmacological interventions.

We have previously observed in a case-control study (215 individuals) that patients with NAFLD have increased levels of biomarkers of atherosclerosis, including PAI1, soluble intercellular adhesion molecule 1, and sCD40L; to extend these observations, we measured, by immunohistochemistry, their hepatic protein expression.[2] We found that liver PAI1 immunoreactivity was significantly associated with disease severity; PAI1 was expressed in hepatocytes as well as in the inflammatory infiltrate.[2] To further evaluate the effect of losartan, an angiotensin II type 1 receptor (AT1R) antagonist, and telmisartan, an AT1R-blocker with insulin-sensitizing properties, on hepatic expression of PAI1 (*Serpine1*), we used a rat model of NAFLD. We found that both drugs reverted fatty liver, but only 12 weeks of losartan strongly reduced hepatic *Serpine1* gene expression.[3] A previous study showed that tumor necrosis factor alpha, which is overexpressed in NAFLD, and renin-angiotensin system coordinately stimulate PAI1 production in hepatocytes.[4] Together, these results suggest that losartan has potential not only in the treatment of NAFLD, but also the associated cardiovascular outcomes, including PAI1 overexpression.

TABLE 1. Pharmacological Targets of SERPINE1 (PAI1)

Drug Name/ Status*	Drug Bank No. and Description	Role/Medical Use	Mechanism/s of Action	Condition (ClinicalTrials.gov Identifier No.)
Urokinase/ approved	DB00013 Low-molecular-weight form of human urokinase	Activator (target)/treatment of embolism, coronary artery thrombosis, and venous and arterial blood clots	Acts on the endogenous fibrinolytic system, cleaving the Arg-Val bond in plasminogen to produce active plasmin	Cholelithiasis Associated With Common Bile Duct Stones (NCT01687959)
Alteplase/ approved	DB00009 Purified human tissue plasminogen activator	Target/glycosylated, 527 residues purified from CHO cells	The protease domain cleaves the Arg-Val bond in plasminogen to form plasmin.	Myocardial Infarction (NCT02182011) Coronary Artery Disease (NCT00868855) Cholelithiasis Associated With Common Bile Duct Stones (NCT01687959) Ischemic Stroke (NCT02572336) Stroke, Acute (NCT01957774) Cardiovascular Risk in Pediatric Cancer (NCT02010190) Obstructive Sleep Apnea (NCT02202811 and NCT00936481) Atherosclerotic Disease (NCT02176941)
Tenecteplase/ Approved	DB00031 527 amino acid glycoprotein	Target/treatment of myocardial infarction and lysis of intracoronary emboli	Binds to fibrin-rich clots through the fibronectin finger-like domain and the Kringle 2 domain	Myocardial Infarction (NCT02182011)
Candesartan/ Approved	DB00796 Class of organic compounds known as biphenyltetrazoles and derivatives	Antagonist	Angiotensin II receptor 1 (AT1) antagonist	Coronary artery disease; Cardiopulmonary bypass; Fibrinolysis; Inflammation (NCT00607672)
Losartan/ Approved	DB00678 Class of organic compounds known as biphenyltetrazoles and derivatives	Antagonist	Angiotensin II receptor 1 (AT1) antagonist	NAFLD in children (NCT01913470)

The list of compounds is based on drugs that specifically target SERPINE1 (Serpin Family E Member 1, PAI-1) either as antagonist or inhibitors, and of which there are current registered clinical trials that include primary and /or secondary outcomes specifically focused on interfering/ acting or targeting PAI1.
Status (*): stands for FDA-approved drugs; #Clinical Trials.gov Identifier extracted from https://clinicaltrials.gov. Drug bank number and description extracted from http://www.drugbank.ca/drugs/.

Table 1 illustrates a full list of pharmacological agents under current investigation targeting PAI1 not only in the treatment of NAFLD, but also related conditions, including obstructive sleep apnea.[5] Collectively, as shown in the work of Ajmera et al.[1] NAFLD pathogenesis involves highly interconnected mechanisms, of which the molecular taxonomy is more complex than the mere accumulation of fat in the liver. In fact, as in many metabolic syndrome components, the pathways involved reflect a low-to-moderate degree of inflammation as simply shown by an increased leukocyte count. Therefore, it is reasonable to assume that NAFLD requires not only precision diagnosis, but also precision treatment.

Silvia Sookoian, M.D., Ph.D.[1]
Carlos J. Pirola, Ph.D., F.A.H.A.[2]
[1]Department of Clinical and Molecular Hepatology
Institute of Medical Research A Lanari-IDIM
University of Buenos Aires–National Scientific and Technical Research Council (CONICET)
Ciudad Autónoma de Buenos Aires, Argentina
[2]Department of Molecular Genetics and Biology of Complex Diseases
Institute of Medical Research A Lanari–IDIM
University of Buenos Aires–National Scientific and Technical Research Council (CONICET)
Ciudad Autónoma de Buenos Aires, Argentina

REFERENCES

1) Ajmera V, Perito ER, Bass NM, Terrault NA, Yates KP, Gill R, et al.; NASH Clinical Research Network. Novel plasma biomarkers associated with liver disease severity in adults with nonalcoholic fatty liver disease. HEPATOLOGY 2017;65:65-77.
2) Sookoian S, Castano GO, Burgueno AL, Rosselli MS, Gianotti TF, Mallardi P, et al. Circulating levels and hepatic expression of molecular mediators of atherosclerosis in nonalcoholic fatty liver disease. Atherosclerosis 2010;209:585-591.
3) Rosselli MS, Burgueno AL, Carabelli J, Schuman M, Pirola CJ, Sookoian S. Losartan reduces liver expression of plasminogen activator inhibitor-1 (PAI-1) in a high fat-induced rat nonalcoholic fatty liver disease model. Atherosclerosis 2009;206:119-126.
4) Takeshita Y, Takamura T, Ando H, Hamaguchi E, Takazakura A, Matsuzawa-Nagata N, et al. Cross talk of tumor necrosis factor-alpha and the renin-angiotensin system in tumor necrosis factor-alpha-induced plasminogen activator inhibitor-1 production from hepatocytes. Eur J Pharmacol 2008;579:426-432.
5) Sookoian S, Pirola CJ. Obstructive sleep apnea is associated with fatty liver and abnormal liver enzymes: a meta-analysis. Obes Surg 2013;23:1815-1825.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.28866

This study was partially supported by grants PICT2010-0441, PICT 2014-0432, and PICT 2014-1816 (Agencia Nacional de Promoción Científica y Tecnológica, FONCyT). S.S. and C.J.P. belong to Consejo Nacional de Investigaciones Científicas (CONICET).

Potential conflict of interest: Nothing to report.

External Validation of the Nomogram for Individualized Prediction of Hepatocellular Carcinoma Occurrence in Patients With Hepatitis C Virus–Related Compensated Cirrhosis

TO THE EDITOR:

We read the article of Ganne et al. enabling an individualized prediction of the risk of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV)-related compensated cirrhosis with great interest. The authors proposed a score based on four variables (age, past excessive alcohol intake, platelet count, and gamma-glutamyl transpeptidase [GGT] serum level) and a time-dependent covariate (sustained virological response).[1] External validation is mandatory before this score becomes widely applied. We took the opportunity of a recent prospective study in patients with HCV-related compensated cirrhosis to evaluate the usefulness of such model to predict HCC occurrence.[2] In our study, three variables were associated with risk of HCC using the Fine and Gray multivariate model (competing risk regression): age (hazard ratio [HR] = 1.06; 95% confidence interval [CI], 1.02-1.09; $P < 0.001$); viral eradication (HR = 0.12; 95% CI, 0.02-0.90; $P = 0.04$); and alcohol intake during follow-up (HR = 3.43; 95% CI, 1.49-7.92; $P = 0.004$). Of note, we identified current alcohol intake, rather than past alcohol intake, as an independent risk factor for HCC. Platelet count used as a continuous variable did not reach statistical significance (HR = 0.99; 95% CI, 0.99-1.00; $P = 0.065$). GGT levels were not available. We categorized age using a cutoff of 50 years, and we included platelet count using two cutoffs (100 and 150 Giga/mm^3). We built two models. In the first, the weight of each factor was given by the root of HR rounded off to the nearer integer. The root of HR was chosen to avoid giving too much weight for a given variable. In the second model, we used the same variables' weight as Ganne et al.'s model. The population was stratified into three groups according to risk of HCC at 5 years. In the first model, risks of HCC were 1.5% (95% CI, 0.0-4.5), 12.3% (4.2-20.4), and 50.1% (31.0-69.2) in patients with the lowest, intermediate, and highest score ($P < 0.001$; Fig. 1A). In the second model, the corresponding risks were 2.9% (0.0-8.5), 8.6% (2.8-14.4), and 50.1% (31.0-69.2), respectively ($P < 0.001$; Fig. 1B).

Thus, we confirmed that a personalized prediction for risk of HCC occurrence can be made using easily available variables in an independent cohort of patients with HCV-related compensated cirrhosis. However, the weight of each factor differed between Ganne et al.'s study and our own. Hence, the best model for predicting the occurrence of HCC has yet to be defined. Given that alcohol intake and viral eradication can change over time, it is likely that future models