Jan Tack and John M. Carethers, Section Editors

Risk of Recurrent Peptic Ulcer in Patients on Clopidogrel

Clopidogrel, an inhibitor of platelet aggregation through inhibition of an ADP receptor on platelets, is recommended as an alternative to aspirin in patients with unstable angina pectoris or with non–ST-segment elevation myocardial infarction. However, earlier studies have shown a high rate of peptic ulcer bleeding in patients with a history of peptic ulcer taking clopidogrel. The mechanism underlying recurrent peptic ulcer bleeding during clopidogrel therapy is unclear, but animal studies suggest that platelet adenosine diphosphate (ADP)-receptor antagonist may inhibit ulcer healing through suppression of the release of platelet-derived growth factors. The optimal prevention of recurrent peptic ulcer and its complications during clopidogrel therapy also has not been addressed. Proton pump inhibitor therapy seems a logical choice, but the interaction between clopidogrel and proton pump inhibitors has been a matter of controversy lately: Activation of clopidogrel, which is a prodrug, involves CYP2C19 isoenzymes, and it has been speculated that this may be inhibited by some proton pump inhibitors.

In this issue of GASTROENTEROLOGY, Hsu et al report the results of a prospective, open-label trial to assess whether proton pump inhibitor therapy can prevent recurrent peptic ulcer or ulcer complications in patients treated with clopidogrel. In this 6-month study, atherosclerotic patients with a history of peptic ulcer disease were randomized to clopidogrel alone or esomeprazole plus clopidogrel. Patients at risk for ischemia who were treated with clopidogrel for ≥2 weeks, who needed long-term antiplatelet therapy, with an endoscopically documented history of gastroduodenal ulcer, and who had a negative upper endoscopy were randomized to esomeprazole 20 mg before breakfast and clopidogrel 75 mg at bedtime, or clopidogrel 75 mg at bedtime for 6 months. Genotyping of CYP2C19 was performed at inclusion in those who gave consent for genetic testing. Nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, anticoagulants, corticosteroids, misoprostol, H2 blockers, and sucralfate were prohibited. Patients who were positive for *Helicobacter pylori* infection received 7-day triple therapy (esomeprazole, amoxicillin, and clarithromycin) first with a control urea breath test after 4 weeks. Those not eradicated received quadruple therapy (esomeprazole, bismuth subcitrate, tetracycline, and metronidazole). The urea breath test was repeated after the 6-month study period. Patients were followed clinically every month. Follow-up endoscopy with biopsy for urease test was performed in cases of persistent dyspeptic symptoms, epigastric pain, hematemesis or melena, and at the end of month 6. The primary end point was the recurrence of endoscopically documented peptic ulcer during the 6-month period. Secondary end points were the occurrence of peptic ulcer bleeding, the occurrence of unstable angina, acute myocardial infarction or ischemic stroke, and vascular death. In addition, in a subset of patients, blood samples were obtained for platelet aggregation testing before the start (patients already on clopidogrel for ≥2 weeks) and on day 28 of the randomized part of the study.

A total of 165 patients (mean age, 72; 75% men) were randomized to esomprazole plus clopidogrel (n = 83) or clopidogrel alone (n = 82), and both groups were comparable in terms of epidemiology comorbidity and *H pylori* status. Follow-up duration, incidence of dyspeptic symptoms, and total number of endoscopies were comparable in both groups. Recurrence of peptic ulcer occurred significantly more in the clopidogrel alone group compared with clopidogrel plus esomeprazole (11.0 vs 1.2%; $P < .01$), and both duodenal and gastric ulcers were present in the monotherapy group. Failure to eradicate *H pylori* did not account for the peptic ulcer cases, and there was only one case of peptic ulcer bleeding, in a patient treated with clopidogrel

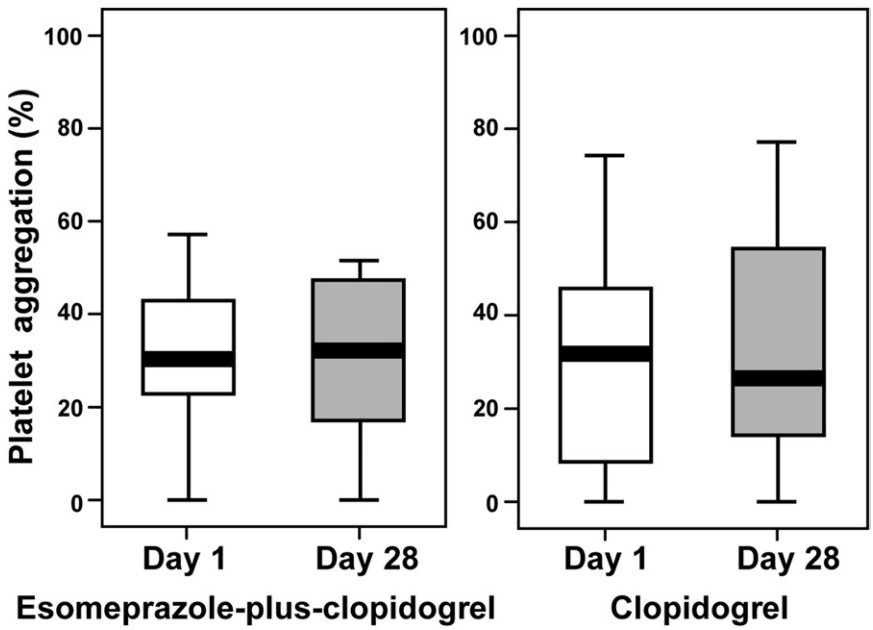

Figure 1. Mean ADP-induced platelet aggregation on days 1 and 28.

alone. There were no significant differences in the combined risk of unstable angina, acute myocardial infarction, and ischemic stroke between both groups, and no vascular deaths occurred. However, patients with reduced-function alleles of CYP2C19 had a higher combined ischemic risk than those with full-function alleles (7.5% vs 0.0%; $P < .05$). No significant differences between platelet aggregation test results on day 1 and day 28 were found in either of the 2 groups (Figure 1).

This prospective, open-label, randomized study showed that adding esomeprazole prevents the high rate of recurrent ulcer in clopidogrel users with a history of peptic ulcer. In addition, there were no signs of decreased inhibition of platelet aggregation and no difference in ischemic events occurred in either group.

See page 791.

Menopause and Hepatitis C Therapy

Important gender-related differences have been observed in the clinical course of chronic hepatitis C virus (HCV) infection, including a more rapid progression to fibrosis in men and inconsistent findings of a better response to antiviral therapy in women. The sex hormonal state seems to be an important contributor to these gender differences, because the rate of liver fibrosis and the risk of developing hepatocellular cancer increase after menopause in women with hepatitis C, and estrogen replacement therapy slows the progression of liver fibrosis. It is unclear whether menopause affects the response to antiviral therapy in hepatitis C.

In this issue of GASTROENTEROLOGY, Villa et al report the results of a prospective study that analyzed the impact of menopause on sustained virologic response (SVR) and on histologic features in women with HCV receiving standard antiviral therapy with pegylated interferon and ribavirin. Consecutive patients with compensated liver disease and detectable HCV RNA plasma levels and no previous HCV treatment were recruited from 2 centers in Italy. All patients had undergone a liver biopsy within one year prior to enrolment. Demographic features, gynecologic and obstetric history, routine laboratory tests, and serum cytokine levels (tumor necrosis factor-α and interleukin [IL]-6) were obtained at enrollment. Menopause was defined as no menstrual periods for 12 consecutive months. Standard antiviral treatment consisted of pegylated interferon (interferon α-2a 180 μg/week, or interferon α-2b 1.5 μg/kg per week; 48 weeks for genotype 1 and 4 and 24 weeks for genotype 2 and 3) and ribavirin (1000 to 1200 mg/d according to body weight). The primary end point, SVR, was defined as undetectable HCV RNA 6 months after the end of antiviral therapy.

A total of 1000 patients were recruited: 558 men and 442 women, 274 of whom were menopausal. Fifty-four women had received hormone replacement therapy for an median duration of 5 years. At baseline, menopausal women had significantly more histologic liver damage than women of reproductive age, with a significantly higher fibrosis score [1.4 (1.0) vs 2.0 (1.0); $P = .002$] and a higher prevalence of cirrhosis (11.0% of late menopausal vs 1.7% of nonmenopausal women; $P = .001$). The length of estrogen deprivation was an independent risk factor for fibrosis. In addition, menopause was associated with a higher prevalence of metabolic disturbances (elevated glucose and cholesterol) and correlated with the grade of necro-inflammation and steatosis on liver biopsies. The plasma levels of IL-6 and hepatic expression of tumor necrosis factor-α were significantly higher in postmenopausal women compared with women of reproductive age (Figure 2).

A total of 838 patients completed the antiviral treatment program. SVR was obtained in 46% of menopausal women compared with 67% of women of reproductive age ($P < .0001$). Compared with men, women of reproductive age had a significantly lower risk of SVR failure ($P < .0001$), although it was similar for menopausal women (P = NS). In multivariate analysis, early menopause [odds ratio (OR), 8.055; 95% confidence interval (CI), 1.834–25.350], cholesterol levels (OR, 0.967; 95% CI, 0.943–0.991), gamma-glutamyl transpeptidase levels (OR, 2.165; 95% CI, 1.3643–0.436) and genotype 1/4 (OR, 3.861; 95% CI, 2.433–6.134) were independent predictors of the risk of SVR failure.

This prospective cohort study in patients with HCV demonstrated that menopause is associated with more severe liver damage and with a significantly lower likelihood of achieving SVR after standard antiviral therapy. The authors hypothesize that menopause is associated with a proinflammatory state that enhances

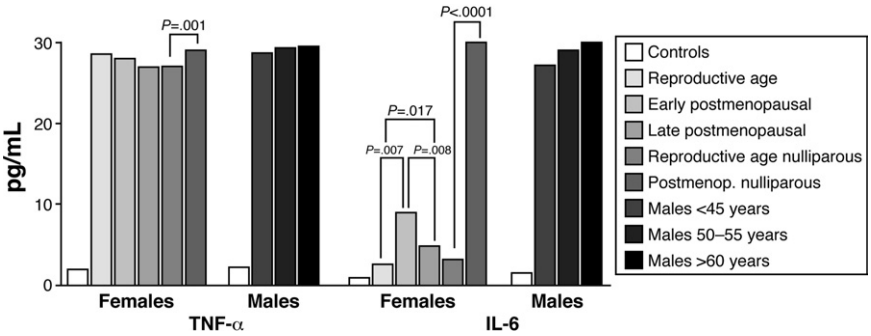

Figure 2. Serum levels of tumor necrosis factor-α and IL-6 in patients with HCV and in matched controls.