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Abstract SY26-02: SWOG S0701 phase III randomized trial of three antibiotic regimens to eradicate helicobacter pylori: efficacy and failure at one year

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Abstract

Background: Gastric cancer is the fourth most common cancer and the second cause of cancer death worldwide. In several Latin American countries, it is the most common cancer and the most common cause of cancer death in men and women combined. Infection with *H. pylori* (Hp) is associated with the development of gastric carcinoma in many parts of the world including Latin America and is thought to be one of the causative agents. We conducted a clinical trial designed to test the effectiveness of three antibiotic regimens for Hp eradication in seven sites in Latin America while assessing feasibility, and the possibility of identifying a direction for future chemoprevention trials of gastric cancer.

Methods: Under a locally IRB approved clinical protocol and signed informed consent requirement, 1852 adults (ages 21-65 years) from the general populations of Chile (Santiago), Colombia (Túquerres), Costa Rica (Guanacaste), Honduras (Copán), México (Obregon and Tapachula), and Nicaragua (León) were screened for the presence of Hp infection with the urea breath test (UBT). 79.4% were positive. 1463 participants consented to be randomized to one of three regimens administered twice a day: 14 days of lansoprazole 30mg, amoxicillin 1,000mg, and clarithromycin 500mg (triple 14d); 5 days of lansoprazole 30mg and amoxicillin 1,000mg followed by 5 days of lansoprazole 30mg, clarithromycin 500mg, and metronidazole 500mg (sequential 10d) or 5 days of lansoprazole 30mg, amoxicillin 1,000mg, and clarithromycin 500mg, and metronidazole 500mg (concomitant 5d). Response was assessed at 6-8 weeks after treatment by UBT. Recurrence at one year was also assessed by UBT. Results are presented by UBT testing and by all participants enrolled (intention-to-treat (ITT)) analysis. 123 (30.8%) patients who did not return for UBT testing were presumed failures at one year. Studies of HP virulence, pepsinogens I and II, as well as inflammatory cytokines, are in progress.

Results: Participant characteristics were similar in the three treatment groups. At 6-8 weeks after treatment, UBT was negative in 1133/1414 (80.1%) patients who underwent follow-up UBT and in 1133/1463 (77.4%) of all participants enrolled. The triple 14d regimen was the superior ($p = 0.008$) regimen among all who had repeat UBT and in the ITT group ($p = 0.005$). The estimated fraction remaining free of infection at one year was 79.3% among participants followed by UBT, and 72.7% for all participants enrolled in the study (Table 1). At one year, in those patients with a negative UBT at 6-8 weeks, Hp recurrence was observed in 11.5%. The risk of infection was greater by site - worse in Chile and Colombia- ($p < 0.0001$), age - worse in the younger - ($p = 0.03$), education - worse in the poorly educated - ($p = 0.02$) and household overcrowding - worse in more crowded households - ($p = 0.007$). Gender, prior antibiotic use, water source and sanitation were not significant factors. By multivariate analysis, the most important predictors of Hp recurrence at one year were study site ($p < 0.0001$), younger age ($p < 0.001$) and crowded households ($p = 0.003$).

Conclusions: This is the largest, prospective, randomized clinical trial ever conducted to treat Hp. The trial was successful in recruiting participants, as well as conducting and monitoring trial treatments and outcomes in 6 Latin American countries. We demonstrated greater treatment efficacy of the triple 14d antibiotic regimen at 6-8 weeks, but a one year 11.5% recrudescence rate regardless of antibiotic regimen. Study site, younger age and crowded households are important factors associated with Hp recurrence at one year. The recurrence rate at one year is concerning, and points to the necessity of conducting additional studies of the molecular biology and pathogenesis of Hp before launching definitive chemoprevention trials of gastric cancer. Given the unique prevalence of gastric cancer and other infection-related cancers in Latin America, we propose that Latin America investigators consider the formation of an independent Cancer Cooperative Group to facilitate research involving cancer. Just as the United States wisely invested in the development of cancer cooperative groups in Europe (European Organization for Research and Treatment of Cancer - EORTC) and in Canada (National Cancer Institute of Canada Clinical Trials Group - NCIC-CTG), we believe that the time has come for consideration of the creation of a cancer cooperative group in Latin America with financial support from the National Cancer Institute.

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Table 1. *H. pylori* eradication overall and by arm at Six - Eight Weeks and One Year

	Definitive UBT n/N (%) p	Total Population n/N (%) p
Six Weeks	1133/1414 (80.1)	1133/1463 (77.4)
	$p=0.008$	$p=0.005$
Triple 14d	401/475 (84.4)	401/488 (82.2)
Concomitant 5d	360/471 (76.4)	360/489 (73.6)
Sequential 10d	372/468 (79.5)	372/486 (76.5)
One Year*	1059/1335 (79.3)	1063/1463 (72.7)
	$p=0.57$	$p=0.28$
Triple 14d	364/452 (80.5)	364/488 (74.6)
Concomitant 5d	342/440 (77.7)	343/489 (70.1)
Sequential 10d	353/443 (79.7)	356/486 (73.3)

*One Year Definitive UBT population requires results at both 6-week and 1-year visits; excludes 5 patients that did not have a 6-week UBT, but provided definitive UBT at 1-year.