Isoniazid Prophylaxis against Tuberculosis in Children

TO THE EDITOR: The results of the study by Madhi et al. (July 7 issue)1 contradict those of a study in which isoniazid prophylaxis reduced mortality and the incidence of tuberculosis by 54% and 79%, respectively,2 in children infected with the human immunodeficiency virus (HIV). The authors suggest that the findings reported in the 2007 study may have resulted from the response of patients with undiagnosed pulmonary tuberculosis to isoniazid monotherapy. This suggestion may be plausible, since childhood tuberculosis is difficult to diagnose. However, all children were carefully screened for tuberculosis at enrollment, at which time 13% received a diagnosis of pulmonary tuberculosis.3 In addition, the results of our recently published long-term study indicate that pulmonary tuberculosis occurred throughout the 5-year study period and further support the efficacy of isoniazid with antiretroviral therapy for the prevention of tuberculosis.3 Differences in patient populations and methods, particularly the use of prophylaxis after exposure to an adult with tuberculosis (a practice rigorously followed by Madhi et al.), may explain the differences. However, the tracing of contacts is poorly conducted in tuberculosis programs, and this strategy is unlikely to be feasible in countries with a high prevalence of tuberculosis. We concur that for HIV-exposed children who have excellent follow-up, prophylaxis is ineffective; however, for HIV-infected symptomatic children receiving care through the public health system in developing countries, isoniazid prophylaxis can offer substantial benefit and protection against tuberculosis.2,3

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THE AUTHOR REPLIES: The differences between our results and those of other researchers, such as the studies by Zar et al. and Frigati et al. cited above, underscore the importance of using great care when generalizing beyond the population under study. Zar and Lombard state that the predominant number of children they enrolled were
not infected with Mycobacterium tuberculosis, and they base this statement on the results of a non-reactive tuberculin skin test, which probably had poor sensitivity for the exclusion of underlying M. tuberculosis infection in their population of children, among whom 82% were moderately to severely immunocompromised and 44% were acutely ill when screened. Considering that it takes 2 to 3 months for tuberculosis to develop after M. tuberculosis infection, the differences in mortality and incidence of tuberculosis observed within 2 months after randomization in the study by Zar et al. indicate that many children may have had underlying infection with M. tuberculosis, which could have been treated in the group receiving isoniazid. Consequently, we disagree that the benefit of isoniazid extends to all group receiving isoniazid. Since publication of their article, the authors report no further potential conflict of interest.


ABVD versus BEACOPP for Hodgkin’s Lymphoma

TO THE EDITOR: Viviani and colleagues (July 21 issue) compared the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) with an escalated BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, with higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide) for initial treatment in patients with advanced-stage Hodgkin’s lymphoma. They concluded that these initial treatment strategies had equivalent rates of long-term overall survival. This conclusion contradicts that of the HD9 study by Diehl and colleagues, which showed superior overall survival with the BEACOPP regimen as compared with a COPP–ABVD regimen.

We are concerned about the emphasis on overall survival (a secondary end point) in a study designed to examine freedom from first progression. The HD9 study was larger than the current study (727 patients vs. 331 patients), had a longer follow-up period (median, 111 months vs. 61 months), and had numerically higher success rates in salvage treatment after ABVD failure (overall survival >50% in HD9 vs. durable complete responses of 33% in the study by Viviani and colleagues). Using the hazard ratio and P value provided in their study, we estimate the 95% confidence interval for the hazard ratio for overall survival to be 0.39 to 1.45. This confidence interval is too wide to draw conclusions about overall survival at this time. Until more mature follow-up data are available, the analysis cannot be interpreted to support the claimed equivalence in overall survival.

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