Correspondence

To the editor:

Early treatment with low-dose aspirin is effective for the prevention of preeclampsia and related complications in high-risk patients selected by the analysis of their historic risk factors

Brenner recently reviewed thrombophilia-related placental vascular complications, notably including preeclampsia and intrauterine growth restriction, and dealt boldly with the question of the potential benefit of aspirin in prevention of preeclampsia, claiming it was raised and refuted in the 1980s. Of course, when preeclampsia occurs in association with factor V (FV) Leiden mutation, factor II 20210G>A, or methylenetetrahydrofolate reductase TT polymorphisms, a specific treatment is required. However, the efficacy of low-dose aspirin in prevention of preeclampsia and related complications was still recently confirmed, and an abundant literature contributed to define now the groups of women who can benefit from low-dose aspirin.

This effect was first demonstrated in high-risk patients accurately selected by close analysis of their historic risk factors. In these first trials, the approach of the investigators was justified in view of the low mean birth weight or high preeclampsia incidence in the placebo groups, and the gain was substantial. Subsequently, several large-scale trials including heterogeneous groups of women at low or moderate risk aimed to test the preventive action of low-dose aspirin either in a high proportion or even in the whole population of the pregnant women. Moreover, gestational age at entry was very variable, until 32 weeks of gestation. Given the low incidence of preeclampsia and the normal mean birth weight in the placebo groups, these large trials not surprisingly either reported a mild benefit or were negative. However, some of them usefully determined that the specific risk attributable to such conditions as primiparity, twin pregnancy, and nonsevere diabetes or hypertension can probably not be avoided by means of low-dose aspirin. In the complex network of the mechanisms involved in the pathogenesis of preeclampsia and related disorders, thromboxane is probably one of the factors leading from defective placentation and placental ischemia to platelet aggregation and placental thrombosis and finally to the clinical stage of the disease. Low-dose aspirin selectively inhibits thromboxane production in the woman’s circulation, and this inhibition parallels the clinical effect. However, the abnormalities of the uteroplacental circulation development that constitute uteroplacental insufficiency are early established. So, the early excess of placental production of thromboxane reported in women with uteroplacental insufficiency may explain that low-dose aspirin only acts optimally when aspirin treatment is started before placentation is completed, and clinical data support this view. Thus, the baseline risk of preeclampsia or intrauterine growth retardation should be estimated and low-dose aspirin started early on the presence of significant historic risk factors, such as previous severe preeclampsia or moderate to severe renal insufficiency. A 2-stage Doppler artery screening in first and second trimester could also define a high-risk population, and promising results have been published for aspirin prevention with first-trimester uterine artery Doppler selection in high-risk pregnancies.

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References


Response:

Role of aspirin in women with thrombophilia

Carbillon and Uzan suggest that aspirin has a positive effect on prevention of preeclampsia in selected high-risk patients. Since my review was focused on management of placental vascular complications in women with thrombophilia, the role of aspirin was only briefly mentioned.

In women with antiphospholipid syndrome and previous complications, aspirin is given with unfractionated heparin (UFH) or low–molecular-weight heparin (LMWH). However, whether a regimen of UFH or LMWH alone without aspirin is sufficient has not been adequately determined in this setting.

The association of inherited thrombophilia with placental vascular complications set the stage for antithrombotic prophylaxis. Aspirin alone has not been found to be of significant value in thrombophilic women with previous pregnancy complications.
Moreover, aspirin crosses the placenta into the fetus and combinations of UFH or LMWH with aspirin may also increase bleeding tendency in the mother. Thus, the routine use of aspirin in thrombophilic women cannot be advocated.

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To the editor:

Natural course of HTLV-1 carriers with monoclonal proliferation of T lymphocytes ("pre-ATL") in a 20-year follow-up study

Previously we reported that asymptomatic human T-cell lymphotropic virus type I (HTLV-1) carriers with a monoclonal proliferation of HTLV-1–infected T cells ("pre–adult T-cell leukemia [ATL]") could account for about 1.7% among a total of HTLV-1 carriers in Japan, and that the pre-ATL subjects had a high potential to develop overt adult T-cell leukemia/lymphoma (ATL/L) and a poor prognosis. Here we report a further analysis of 50 pre-ATL subjects who were enrolled and followed during October 1976 to December 2003 to evaluate their outcomes in Nagasaki prefecture, an endemic area of ATL/L in Japan. Detection assays of the integration band of the HTLV-1 provirus genome were described previously. There were 3 end points evaluated: the development of overt ATL/L, death from ATL/L, and overall survival. The diagnostic criteria for overt ATL/L were based on the Lymphoma Study Group (LSG) classification.

The screening of the pre-ATL subjects from the endemic area of ATL/L in Japan. Detection assays of the integration band of the HTLV-1 provirus genome were described previously. There were 3 end points evaluated: the development of overt ATL/L, death from ATL/L, and overall survival. The diagnostic criteria for overt ATL/L were based on the Lymphoma Study Group (LSG) classification. Time-to-event probability was estimated by the Kaplan-Meier methods. Entry age, sex, white blood cell (WBC) count, relative lymphocyte (rLy) counts, and relative abnormal lymphocyte (rAbLy) count were considered as potential prognostic factors. Effects of these factors were evaluated by the Cox proportional hazard regression.

Among 50 subjects, 21 (42%) progressed to overt ATL/L (the incidence rate: 48.0 per 1000 person-years), and 31 (62%) died, of whom 21 died from ATL/L itself. The remaining 10 subjects died of opportunistic infections such as Carinii pneumonia or other malignancies (skin carcinoma, lung cancer, etc). In the univariate analyses, subjects with a WBC count more than 9000/μL showed a higher risk for the development of overt ATL/L compared with those with a WBC count less than 9000/μL (hazard ratio [HR], 3.93; 95% confidence interval [CI], 1.50-10.0). The effect did not change even in an adjusted analysis for other factors. A higher rAbLy count (more than 50%) was also associated with the development of overt ATL/L (HR, 3.04; 95% CI, 1.16-7.95). A higher rAbLy count and older entry age (older than 56 years) were marginally associated with overall survival (data not shown). The comparison of the cumulative probability between the 2 groups of WBC counts showed a significant difference in the development of overt ATL/L (85.7% vs 33.0%) and in death from ATL/L (87.0% vs 72.3%), but no difference in the overall survival rate (Figure 1).

Several Japanese cross-sectional surveys reported a crude annual incidence of ATL/L ranging from 50 to 150 per 100 000 HTLV-1 carriers. Although our results may overestimate the risk because we did not take a competing risk of death into consideration, the results indicate that the pre-ATL subjects have a high potential to develop overt ATL/L among HTLV-1 carriers. Notably, most of the subjects with a WBC count above 9000/μL developed overt ATL/L, suggesting that those should be considered as the "early stage of ATL/L." On the other hand, about two thirds of the subjects with a WBC count below 9000/μL never developed overt ATL/L, suggesting that those would be literally in the "premalignant stage." The screening of the pre-ATL subjects from the

References


Figure 1. Kaplan-Meier analyses for 3 end points of interest by 2 categories of white blood cell count. Among 20 subjects with a white blood cell count above 9000/μL, 15 developed overt ATL/L, 15 died from ATL/L, and 1 died from other disease. Among 30 subjects with a white blood cell count below 9000/μL, 6 developed overt ATL/L, 6 died from ATL/L, and 9 died from other causes. All comparisons were performed using the log-rank test. (A) The cumulative probability of the development into overt ATL/L was 85.7% in the group with a white blood cell count above 9000/μL versus 33.0% in the group with a white blood cell count below 9000/μL (P = .0028). (B) The cumulative probability of death from ATL/L was 87.0% in the group with a white blood cell count above 9000/μL versus 72.3% in the group with a white blood cell count below 9000/μL (P = .0048). (C) The overall survival was 12.0% in the group with a white blood cell count above 9000/μL versus 18.0% in the group with a white blood cell count below 9000/μL (P = .20).
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