Appropriate Use of Nevirapine for Long-Term Therapy

To the Editor—The recent article by Sanne et al. [1] described possible risk factors associated with hepatic adverse events that can occur while nevirapine is being taken in a clinical trial. We are concerned about several key issues either overlooked or minimized in the article. It is important to understand that the preliminary results of the FTC-302 study provided the impetus for Boehringer Ingelheim (BI) to conduct a comprehensive analysis of hepatotoxicity in all large BI controlled and uncontrolled studies. This analysis resulted in warnings that female sex and higher CD4 cell count at the initiation of therapy increases the risk of hepatotoxicity, particularly during the first 6 weeks of treatment. This information has been widely communicated through changes to the prescribing information and through BI communications to physicians. Most recently, BI has recommended against the initiation of nevirapine treatment in women with CD4 cell counts <250 cells/mm$^3$ or in men with CD4 cell counts <400 cells/mm$^3$ unless the benefit outweighs the risk (see http://www.fda.gov/cder/drug/advisory/Nevirapine.htm). As shown in figure 1, there is a clear demarcation in the risk of developing nevirapine-associated symptomatic hepatitis at the CD4 cell count cutoffs mentioned above.

In our comprehensive analyses, the frequency of patients with symptomatic hepatic events in the lower CD4 cell count groups (women with counts <250 cells/mm$^3$ and men with counts <400 cells/mm$^3$) was significantly reduced and was consistent with frequencies found in association with other antiretrovirals, including efavirenz (1%–2%). We are concerned that, because study FTC-302 excluded patients with CD4 cell counts <200 cells/mm$^3$, the major predictive factor of hepatic events was removed from consideration, therein biasing the authors’ conclusion that a low body mass index (BMI) is predictive of nevirapine hepatotoxicity.

Additionally, there was only a small number of patients with BMIs <18.5 (4.4% of total), and these accounted for only a small proportion of patients with hepatotoxicity (11.3%). This result suggests that there were other explanations for the high rate of hepatic events observed in this study, including the mean CD4 cell count of 406 cells/mm$^3$ in patients with early events and coadministration of other potentially hepatotoxic medications, including stavudine. Thus, the conclusion that BMI is predictive of nevirapine-associated hepatotoxicity may be spurious, because of a combination of study design, statistical artifact, and the involvement of other factors that were not assessed in the article.

It is also important to emphasize that patients were not monitored for the appearance of rash or hepatotoxicity until after 4 weeks of treatment. This is insufficient, according to current recommendations, especially given that the majority of these events occur during the first 6 weeks of treatment. Likewise, prompt discontinuation of nevirapine is recommended after the onset of grade 3 or 4 rash or constitutional symptoms suggestive of hepatitis. It is possible that recommended monitoring and more-rapid discontinuation of trial medications would have lessened the severity of reactions in some patients in FTC-302.

Although BI has initiated a toxicogenomics program to study the complex relationship between nevirapine and hypersensitivity reactions, we believe that, by making the relatively simple recommendation based on CD4 cell count, there will be a significant reduction in the incidence of nevirapine-associated adverse events. By working to improve nevirapine safety within the standard guidelines for treatment initiation, an important option for

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**Figure 1.** Frequency of early symptomatic hepatic events in controlled and uncontrolled trials with nevirapine. Data are from Boehringer Ingelheim’s Expanded Hepatic Analysis and are included in EU/US VIRAMUNE prescribing information; “early symptomatic events” refers to events occurring during the first 6 weeks of treatment.
antiretroviral therapy is maintained for patients with HIV infection.

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Reply to Leith et al.

To the Editor—In their response to our article [1], Leith et al. [2] from Boehringer Ingelheim (BI) Pharmaceuticals, the manufacturer of nevirapine, argue against our overall conclusion. Briefly, we observed a high incidence of hepatotoxicity (17%) in a large randomized, prospective, controlled trial that included nevirapine as part of combination antiretroviral therapy. On the basis of a multiple regression analysis, we concluded that women with a body mass index (BMI) <18.5 and low albumin levels had a markedly increased risk of developing nevirapine-associated hepatotoxicity, but we did not identify a correlation between the occurrence of hepatotoxicity and high CD4 cell counts, as had been reported by BI.

The analysis completed by BI concluded that the major predictive factor for nevirapine-associated hepatotoxicity was baseline CD4 cell count (>250 cells/mm3 in women and >400 cells/mm3 in men). The data used to derive these results were from 9 randomized controlled trials that primarily enrolled male patients (80%); 63% of the patients were white, 19% were black, and 61% had baseline CD4 cell counts <200 cells/mm3. By comparison, the group of patients treated with nevirapine in the FTC-302 study was primarily female (60%); 78% of the patients were black, and 12% were white. Seventeen percent of the women had baseline CD4 cell counts <250 cells/mm3, and 56% of the men had baseline CD4 cell counts <400 cells/mm3. The population in the FTC-302 study allowed for the assessment of other possible factors associated with hepatotoxicity that were not assessed in previous studies. In our study, we used a definition that was based solely on liver enzymes rather than on symptomatic hepatic adverse events. We observed 53 cases of early hepatotoxicity, 42 in women and 11 in men. Six of the 42 women had baseline CD4 cell counts <250 cells/mm3, and 6 of the 11 men had baseline CD4 cell counts <400 cells/mm3. In our study, immune status at baseline was not predictive of hepatotoxicity, but a BMI <18.5 and a serum albumin level <35 g/L were strong risk factors for the emergence of hepatotoxicity. In the FTC-302 study, 80% of the hepatotoxicity events were detected before week 12, with 34% of these events resolving in spite of continuation of nevirapine treatment.

In the double-blind, placebo-controlled trial FTC-302, contrary to the statement by Leith et al. [2] regarding the monitoring for the appearance of rash or hepatotoxicity, patients were monitored at day 7, day 14, and day 28 (week 4) for adverse events, with laboratory evaluations (including assessment of alanine aminotransferase and aspartate aminotransferase levels) beginning at the week 4 visit. This monitoring schedule was more stringent than that prescribed in the guidance information at the time the study was initiated and did not allow for the prevention of liver failure in 2 patients.

As described in our article [1], a population pharmacokinetics study of nevirapine conducted by De Maat et al. demonstrated a decreased clearance of nevirapine in subjects with lower weight or who were of black race [3]. A recent pharmacogenomic study of nevirapine and hepatotoxicity in patients in FTC-302 found that the risk of hepatotoxicity while taking nevirapine was strongly associated with a multiple drug resistance protein 1 (MDR1) polymorphism that differs in frequency between ethnic populations [4]. Although the BI analysis found a correlation between baseline CD4 cell count and reported toxicities, our analysis and others [5] found no such correlation between CD4 cell count and hepatotoxicity. In conclusion, factors other than, or in addition to, CD4 cell count must play a role in nevirapine-associated hepatotoxicity.

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Postmortem Brain Smear Assessment of Fatal Malaria

To the Editor—The advantages of brain smears over standard histological sections in preserving long sections of capillaries and venules and, thus, allowing quantitative assessment of parasite sequestration in fatal falciparum malaria were first reported by Raja in 1922 [1]. For the past 24 years, we have used a combination of light microscopy, immunofluorescence microscopy, and electron microscopy on postmortem perorbital brain samples and have reported results from >50 fatal cases of malaria [2–4]. We concur with Milner et al. [5] that the procedure is useful but disagree on the subject of quantitation. When light microscopy is used, the brain smear preparation allows a better assessment of the intensity, stage distribution, and intervessel variance of sequestration than do conventional histological sections, which are at a random plane compared with the axis of the vessel being assessed.

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References

Reply to White and Silamut

To the Editor—We appreciate the comments from White and Silamut [1]. We did not cite Raja’s original study [2] in our article [3], because Raja’s study is a report of 4 cases in which smears of brain tissue from patients dying of malaria are compared with the gross appearance of the brain and not with histological appearance. Our own experience has shown that the gross appearance of the brain is not always “classic” (i.e., with a slate gray cerebral cortex and petechial hemorrhages) (figure 1). Raja’s use of brain smears is, however, a good example of using the technique in the context we suggest—that is, when histological analyses are not possible. We do not claim to have discovered a new technique, but we hope that our validation will help to expand its use.

We did not compare intensity, stage distribution, and intervessel variance of sequestration in smears versus histological sections, because our goal was to validate a practical tool for nonpathologists and nonscientists. We did establish that brain smears obtained from a single site (the frontal lobe) could be used to identify patients with significant sequestration as reliably as when the more laboriously obtained histological sections (which require opening of the skull; fixing, embedding, and staining of the tissue; and interpretation by a pathologist) are used. We believe that our validation establishes that brain smears are a sound method for confirming the presence of cerebral sequestration when histological analyses are not possible. In our recent study of fatal malaria in children [4], cases lacking cerebral sequestration of parasites invariably had an additional pathological explanation for death.

Our goal was to expand the capacity to identify significant cerebral sequestration of parasitized red blood cells to clinicians working in malaria-endemic areas where
autopsies and histological analyses are not possible. Because the standard clinical case definition lacks specificity and positive predictive value, this additional information may be useful, both in the context of individual case diagnoses and in interpretation of findings from research studies.

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