Neuropharmacokinetic Heterogeneity of Mefloquine in the Treatment of Progressive Multifocal Leukoencephalopathy

Key words: mefloquine, PML, genetic polymorphisms, pharmacokinetic heterogeneity

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The Authors Reply We appreciate the comment by Nevin on our manuscript. Differences in the pharmacokinetics and pharmacodynamics of pharmacological agents can be found not only among people of different races, but also among people of the same race. Recent research has provided increasing evidence that these differences are due to mutations found in genes encoding related proteins. The relationship between the pharmacokinetics/pharmacodynamics and pharmacogenetics of mefloquine is believed to be of critical importance in examining the therapeutic effects of mefloquine in progressive multifocal leukoencephalopathy (PML).

The clinical trial on the use of mefloquine in the treatment of PML has regrettably been discontinued in the United States (1). One reason given for the discontinuation of that clinical trial was that it included HIV-PML patients. As HAART has been used as a treatment for AIDS in recent years, the resulting immune reconstitution of AIDS patients has dramatically improved the vital prognosis in patients with HIV-PML. Distinguishing whether the improvement in the vital prognosis of PML patients is due to HAART or the anti-JCV effects of mefloquine is thus extremely difficult. The case we previously presented (2) was also that of an HIV-PML patient, however the following developments occurred: a) even after about 3 months of HAART, PML continued to progress, and the patient developed akinetic mutism; b) even after introducing HAART, the CD4+ cell counts remained below 200/μL without showing any increase, and no immune reconstitution was apparent; and c) symptomatic improvement was first observed approximately 5 weeks after the introduction of mefloquine treatment. As a result, we feel confident in the clinical determination that the effect of mefloquine was predominant. However, the possibility that this finding was due to the effects of HAART or an interaction between HAART and mefloquine cannot be completely ruled out. We do not currently have the means to fully verify these possibilities.

Mefloquine treatment needs to be conducted on a larger number of non-HIV-PML patients. In the future, information on genetic polymorphisms of the proteins involved in the pharmacokinetic heterogeneity of mefloquine should be better organized. Using such information, a study on the effectiveness of mefloquine from a pharmacogenetic perspective could be performed. Such a study would entail conducting clinical trials in Japanese patients, many of whom have been found to respond well to mefloquine treatment, as well as conducting comparative studies among patients of different races.

The authors state that they have no Conflict of Interest (COI).

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References