CORRESPONDENCE

Association between Secondary Mutations in Human Immunodeficiency Virus Type 1 Protease and Therapeutic Outcome

To the Editor—Perno et al. [1] report that the number of pretherapy secondary mutations in human immunodeficiency virus (HIV) type 1 protease and the combination of mutations at codons 10 and 36 are associated with poorer outcome for patients commencing protease inhibitor (PI)–based combination antiretroviral therapy (CART). We have a number of concerns relating to these findings.

The statistically significant association of the M36I polymorphism with virologic failure is important, since this polymorphism is highly prevalent in African viruses (subtypes A, C, and D). Other polymorphisms at codons 10, 20, 63, 71, 77, and 93 are also not uncommon. A major implication of the work by Perno et al. [1] is that African patients will do less well on PI-based CART, and, accordingly, it would have been of interest to see subtype data, since many of the isolates with secondary mutations are likely to have been from African patients.

We recently presented data that show that the early virologic and immunologic responses of African and European HIV-positive patients are almost identical [2]. For example, Kaplan-Meier estimates for the proportions achieving virus undetectability by 6 months were 81% for both the European and African groups. The absence of effect of ethnic group persisted after controlling for baseline virus load, baseline CD4 cell count, and drug class in a multivariate Cox regression analysis (P = .5). African and European patients appeared to be equally susceptible to virologic inhibition produced by CART, despite the presence in the African cohort of many of the secondary polymorphisms described by Perno et al. [1].

In addition, we sequenced virus isolates from African patients at baseline and also at the point of CART failure. No association with poorer outcome was found with either total numbers or the presence of individual baseline secondary protease mutations prior to therapy, including at codons 10 and 36 [3]. Further analysis looking at combinations of mutations at baseline showed no association with poorer outcome for patients undergoing PI-based therapy.

Although Perno et al. [1] acknowledged the absence of sequence data from patients in whom therapy failed, they understated the significance of this omission. Patient noncompliance is a major cause of virologic rebound on CART, and without evidence of drug pressure, as indicated by new resistance mutations, the reason for failure remains speculative. In our study, only 50% of the African patients with virologic rebound developed resistance-associated mutations at the point of failure. This suggests that management of adherence is the key issue rather than preexisting polymorphisms.

The findings of Perno et al. [1] are theoretically plausible, and the potential impact of baseline secondary protease mutations is a major concern. However, we suggest that, when considered with our own findings, the case for associating baseline secondary PI mutations with therapeutic outcome remains unproven.

John Frater,1 David Dunn,2 Jonathan N. Weber,1 and Myra O. McClure1

1Jeffreys Research Laboratories, Wright-Fleming Institute, Division of Medicine, Imperial College School of Science, Technology, and Medicine, St. Mary’s Campus, and 2Medical Research Council HIV Clinical Trials Unit, London, United Kingdom

References

Reply

To the Editor—We read with interest the comments by Frater et al. [1] about our recent publication [2] and the results of their study regarding the efficacy of combined antiretroviral therapy in patients carrying non-B human immunodeficiency virus (HIV) subtypes [3]. Other cohort studies have evaluated the association between secondary mutations in HIV protease before initiation of antiretroviral therapy and therapeutic outcome, with discrepant results [4–6]. We therefore agree that more evidence is needed to support the view that widespread resistance testing should be performed for drug-naive patients, to guide the choice of initial therapy.

Additional data would be especially useful for antiretroviral-naive patients infected with non-B subtypes of HIV, in whom many secondary mutations are naturally occurring polymorphisms, as we mentioned in the Discussion section of our article [2, pp. 987–989]. Beyond these needs, which have to be addressed by the scientific community, we feel that some points raised by Frater et al. [1] merit attention for their practical impli-