Human Immunodeficiency Virus Type 1 Hypersusceptibility to Amprenavir In Vitro Can Be Associated with Virus Load Response to Treatment In Vivo

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The human immunodeficiency virus type 1 protease mutation N88S, which is occasionally selected by treatment with nelfinavir or indinavir, confers hypersusceptibility to amprenavir in vitro. The clinical relevance of this observation is unclear. We report a case of N88S developing after virologic failure of both indinavir- and nelfinavir-containing regimens that was managed successfully with a regimen that contained amprenavir.

HIV type 1 (HIV-1) protease mutation N88S has been shown to confer hypersusceptibility to amprenavir in vitro [1, 2]. This mutation is rarely selected by nelfinavir or indinavir in vivo, although the former does frequently select N88D [3]. We describe a patient who developed N88S after having virologic rebound while receiving indinavir- and nelfinavir-containing regimens and who achieved durable virologic suppression while receiving an amprenavir-based regimen.

A 33-year-old man had HIV-1 infection diagnosed in 1992. He started receiving sequential antiretroviral monotherapy, first with zidovudine, then didanosine. In 1995, he developed peripheral neuropathy, myelopathy, and chronic disseminated varicella that required treatment with foscarnet. Because of the peripheral neuropathy, his antiretroviral treatment was changed back to zidovudine monotherapy. In 1996, he developed disseminated *Mycobacterium avium* complex infection. The patient had a CD4+ cell count of 8 cells/mm3 and a plasma HIV-1 RNA level of 322,700 copies/mL, and lamivudine was added to zidovudine in February 1996; indinavir was added in May 1996. By December 1996, the patient had significantly improved clinically: he had a CD4+ cell count of 106 cells/mm3 and a plasma HIV-1 RNA level of <400 copies/mL (figure 1). In April 1997, his plasma HIV-1 RNA level rebounded to 8980 copies/mL and his CD4+ cell count was 105 cells/mm3. Antiretrovirals were switched to stavudine, nevirapine, and nelfinavir. His virus load was <400 copies/mL 1 month after this switch, but in July 1997, it quickly rebounded to 10,800 copies/mL, with a concomitant CD4+ cell count of 172 cells/mm3. Antiretroviral therapy was not modified, and, during the next 2 years, his plasma HIV-1 RNA levels remained between 4000 copies/mL and 13,000 copies/mL, and there was a steady increase in the CD4+ cell count. His clinical status continued to be favorable, and the patient returned to full-time employment.

In September 1999, HIV-1 genotypic resistance testing (Specialty Laboratories; Santa Monica, California) was performed when the patient’s plasma HIV-1 RNA level was 4840 copies/mL and his CD4+ cell count was 299 cells/mm3. The following reverse-transcriptase inhibitor resistance mutations were found: D67N, K70R, K103N, Y181C, T215Y, and K219Q. The protease inhibitor resistance mutations were L10I, I64V, V77I, and N88S. Given these results and a report that the protease N88S mutation was associated with hypersusceptibility to amprenavir in vitro [1], the antiretroviral regimen was switched on 5 October 1999 to stavudine, 40 mg b.i.d.; abacavir, 300 mg b.i.d.; ritonavir, 400 mg b.i.d.; and amprenavir, 750 mg b.i.d. Phenotypic resistance testing (ViroLogic; South San Francisco, California) of the plasma HIV-1 RNA sample from 14 September 1999 subsequently revealed that the IC50 (inhibitory concentration for 50% of isolates) of amprenavir was 10-fold lower than that of a wild-type control (table 1). The patient tolerated the new regimen well, and his plasma HIV-1 RNA levels decreased to <400 copies/mL 1 month after changing treatment and <50 copies/mL 2 months after the change. All subsequent plasma HIV-1 RNA measurements have been at <50 copies/mL; the most recent was recorded in October 2001 (24 months after switching the treatment regimen), when the patient’s CD4+ cell count was 602 cells/mm3.

Amprenavir is likely to have been the most active component of the salvage regimen in this patient. Other studies have found

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Figure 1. CD4+ cell count and plasma HIV type 1 (HIV-1) RNA responses to antiretroviral therapy. Genotyping results at particular time points are shown in insets. ABC, abacavir; APV, amprenavir; AZT, zidovudine; d4T, stavudine; IDV, indinavir; NFV, nelfinavir; NVP, nevirapine; PR, protease inhibitor resistance mutations; RT, reverse-transcriptase inhibitor mutations; RTV, ritonavir; 3TC, lamivudine.

Table 1. Results of phenotypic resistance testing, 5 October 1999.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fold decrease in susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>2.1</td>
</tr>
<tr>
<td>Didanosine</td>
<td>0.7</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3.9</td>
</tr>
<tr>
<td>Stavudine</td>
<td>1.7</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>36.4</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>33.6</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>0.1</td>
</tr>
<tr>
<td>Indinavir</td>
<td>2.5</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>14.6</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>0.6</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*a* Inhibitory concentration for 50% (IC50) of the patient isolates/IC50 for wild-type control.

that virologic responses to abacavir in vivo are attenuated when extensive zidovudine resistance is present, such as the 4 zidovudine-selected mutations noted here [4, 5]. However, it is possible that abacavir contributed to the activity of the combination started in October 1999 in the suppression of HIV-1, given the moderate 2.1-fold resistance to abacavir noted in the phenotypic assay. The contribution of stavudine to the activity of this combination is similarly questionable, given that use of this drug was continued from the failing regimen and there were several zidovudine-selected mutations [6] and 1.7-fold stavudine resistance. Recent data have led to stavudine resistance now being considered clinically relevant at an increase above wild type that is lower-fold than that for abacavir resistance [7]. It is possible that ritonavir is contributing to the activity of the current regimen, given the dosage used and the lack of phenotypic resistance; however, there is significant overlap between resistance to indinavir and resistance to ritonavir, and this patient had experienced virus rebound while receiving an indinavir-based regimen [8]. The excellent response to the addition of ritonavir-boosted amprenavir suggests that further study of the clinical relevance of amprenavir hypersusceptibility associated with the protease mutation N88S is warranted, especially because it may be a signature mutation in vitro for the investigational protease inhibitor, atazanavir (BMS-232632; Bristol-Myers Squibb) [9]. This drug is currently being evaluated in phase II and III trials. Given the therapeutic challenge posed by cross-resistance among protease inhibitors in treatment-experienced patients, new options for sequencing these drugs would be most welcome.
References