Case report

The role of raltegravir in the treatment of HIV-2 infections: evidence from a case series

Kevin Peterson1*, Jean Ruelle2, Marc Vekemans1, Frederick P Siegal3, Jane R Deayton4, Robert Colebunders1,5

1Department of Clinical Science, Institute of Tropical Medicine, Antwerp, Belgium
2Institute of Experimental and Clinical Research (IREC), Université Catholique of Louvain, Brussels, Belgium
3Mount Sinai School of Medicine, Mount Sinai Medical Center, New York, NY, USA
4Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
5Medical Faculty, University of Antwerp, Antwerp, Belgium

*Corresponding author e-mail: kpeterson@itg.be

We describe five patients with HIV-2 infection (four antiretroviral-experienced and one antiretroviral-naive) treated with a regimen containing raltegravir. All responded to treatment as demonstrated by viral load and CD4+ T-cell count monitoring. Our series confirms the clinical effectiveness of raltegravir in HIV-2-infected patients when given with other antiretrovirals to which the virus is susceptible.

Introduction

Therapies optimized for HIV-1 infection can be insufficiently active against HIV-2 infection [1]. We report detailed clinical and laboratory histories of five HIV-2-infected patients successfully treated with raltegravir (RAL) on an optimized background regimen. Four were treatment-experienced and one was treatment-naive. Key elements of the antiretroviral (ARV) history and response are summarized in Table 1, with detailed patient histories described below. Pertinent resistance mutations are based on the Rega Algorithm, version 8.0.2 [2].

Case histories

Patient 1
A 55-year-old woman from West Africa was diagnosed with HIV-2 in 1990. She eventually developed diarrhoea and weight loss and in 2002 started zidovudine (AZT), lamivudine (3TC) and nelfinavir (NFV), replacing AZT after a couple of months with stavudine (d4T) because of headache and nausea. Viral loads (VLs) ranged between 2,000 and 23,000 copies/ml, her CD4+ T-cell counts drifted to a nadir of 181 cells/μl, and the patient switched in 2003 to abacavir (ABC), ritonavir-boosted lopinavir (LPV/r) and d4T, substituting tenofovir (TDF) for d4T in 2005. Her VLs during this time swung between undetectable (UD) and >110,000 copies/ml during the first 2 years, and between UD and 23,000 copies/ml between 2005 and 2010. She later reported that during this time she had never refrigerated her soft-gel LPV/r capsules. The patient developed the Q151M and M184V mutations, yet stayed on this regimen for 5 years with CD4+ T-cell counts remaining at approximately 300 cells/μl. In August 2010, her VL increased to 61,000 copies/ml with the mutations listed in Table 1, and her CD4+ T-cell count fell to 282 cells/μl. In October 2010, the patient switched to ritonavir-boosted darunavir (DRV/r) and RAL with AZT/3TC. After 1 year, the VL was UD and the CD4+ T-cell count was 428 cells/μl.

Patient 2
A 50-year-old man from Senegal was diagnosed with HIV-HBV-coinfection in 1987, determined 1 year later to be HIV-2. His CD4+ T-cell counts remained >750 cells/μl until 1993. By 1999, they were hovering around 150–200 cells/μl and he started nelfinavir (NFV) with AZT/3TC. This treatment was maintained for 3 years, from 1999 to 2003, without any appreciable change in his CD4+ T-cell count. At the end of this time a genotypic resistance test showed the mutations in Table 1. Over the next 3 years his regimen was ABC, didanosine (ddI) and TDF. During this time he also had a brief exposure to 3TC, 3 weeks of ddI monotherapy and a 3-week complete treatment interruption. Viral control was intermittent with viraemia occasionally >10,000 copies/ml and his CD4+ T-cell counts decreased to <100 cells/μl. He switched to his third regimen, TDF/LPV/r and remained...
on that from 2006–2009; he was virally suppressed except for one measurement >2,000 copies/ml. During this time his CD4+ T-cell counts continued to decrease, reaching a nadir CD4+ T-cell count of 55 cells/μl in 2009, at which time he also had a VL >2,000 copies/ml. He then switched to TDF, emtricitabine (FTC), DRV/r and RAL. After 2 years the VL was UD and the CD4+ T-cell count was 293 cells/μl.

Patient 3
A 58-year-old woman who had received multiple blood transfusions in West Africa was initially diagnosed as HIV-1-infected in 1996. At the time of her diagnosis her CD4+ T-cell count was 70 cells/μl (12% of CD3+ CD4+ T-lymphocytes). She started indinavir (IDV) with AZT/3TC in 1997, and substituted NFV for IDV in 1998. Her symptoms resolved and her CD4+ T-cell counts rose, before falling again. She developed chronic diarrhoea, and her regimen was changed to TDF, FTC, and ritonavir-boosted atazanavir (ATV/r) in September 2004. The absence of a detectable HIV-1 VL in the face of progressive CD4+ T-cell count decline resulted in a workup that led to her HIV-2 diagnosis in June 2007 and LPV/r was substituted for ATV/r, however adherence to a twice-daily regimen was challenging and she switched back to ATV/r. In November 2007 her VL was 136,300 copies/ml. In March 2008, the regimen was changed to AZT/3TC/TDF/DRV/r/RAL. After 3.5 years, the VL was 55 copies/ml and the CD4+ T-cell count was 321 cells/μl.

Patient 4
A 41-year-old woman from Ghana was diagnosed with HIV-2 in January 2004 with a CD4+ T-cell count of 96 cells/μl and a VL of 5,030 copies/ml. She started AZT/3TC/LPV/r in February 2004. After 3 months, when she switched from AZT to ABC for toxicity reasons, her VL was UD. ABC was switched to TDF 2 months later by the patient's choice. The CD4+ T-cell count climbed to 292 cells/μl after 1 year of therapy, and declined afterwards, while the viral load rose. The viral mutations selected for are listed in Table 1. Therapy was changed in September 2009 to AZT/3TC/ABC/SQV/r/RAL at which time the patient had a CD4+ T-cell count of 53 cells/μl. Her VL on this regimen, otherwise UD, was twice detectable <200 copies/ml, and after 2 years the VL was 50 copies/ml and the CD4+ T-cell count is 365 cells/μl.

Patient 5
A 33-year-old woman, without a clear connection to West Africa, was diagnosed with HIV-2 in March 1999, with a VL of 170 copies/ml and a CD4+ T-cell count of 360 cells/μl. As CD4+ T-cell counts dropped to 220 cells/μl, she switched from AZT to ABC for toxicity reasons, her VL was UD. ABC was switched to TDF 2 months later by the patient's choice. The CD4+ T-cell count climbed to 292 cells/μl after 1 year of therapy, and declined afterwards, while the viral load rose. The viral mutations selected for are listed in Table 1. Therapy was changed in September 2009 to AZT/3TC/ABC/SQV/r/RAL at which time the patient had a CD4+ T-cell count of 53 cells/μl. Her VL on this regimen, otherwise UD, was twice detectable <200 copies/ml, and after 2 years the VL was 50 copies/ml and the CD4+ T-cell count is 365 cells/μl.

Discussion
Our series confirms the clinical effectiveness of RAL in treatment-experienced patients with HIV-2 infection when given with other ARVs to which the virus is susceptible. All five of these patients had a detectable VL prior to RAL-based ART.

Several case reports have been published of treatment-experienced patients treated with a RAL-containing regimen. These are summarized in Table 2. Differences in the HIV-2 integrase region may lower the resistance barrier to integrase inhibitors compared

Table 1. Baseline antiretroviral history, raltegravir regimen and virological and immunological outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior ARV exposure and resistance mutations</th>
<th>RAL regimen</th>
<th>Follow-up duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AZT, 3TC, d4T, ABC, TDF, NFV and LPV/r over 8 years with RT mutations K65R, N65S/T, V75M, V111I, Y115F and S215T, and PR mutations V33I, V47A, V62A, I89V and L99F at RAL initiation, and RT mutations Q151M and M184V previously seen</td>
<td>AZT/3TC/DRV/r plus RAL</td>
<td>1 Year</td>
<td>VL fell from 61,000 copies/ml to UD; CD4+ T-cell counts rose from 282 to 428 cells/μl</td>
</tr>
<tr>
<td>2</td>
<td>AZT, 3TC, ABC, d4T, NFV and LPV/r over 10 years with RT mutations Q151M and M184V seen earlier</td>
<td>TDF/FTC/DRV/r plus RAL</td>
<td>2 Years</td>
<td>VL fell from &gt;2,000 copies/ml to UD; CD4+ T-cell counts rose from 55 to 293 cells/μl</td>
</tr>
<tr>
<td>3</td>
<td>AZT, 3TC, TDF, FTC, IDV, NFV and ATV/r over 12 years</td>
<td>AZT/3TC/TDF/DRV/r plus RAL</td>
<td>3.5 Years</td>
<td>VL fell from 136,000 to 55 copies/ml; CD4+ T-cell counts rose from 42 to 321 cells/μl</td>
</tr>
<tr>
<td>4</td>
<td>AZT, 3TC, ABC, TDF and LPV/r over 5 years with RT mutations A62V, K65R, N69S, K70N and S215L, and PR mutations V33I and V47A</td>
<td>AZT/3TC/ABC/SQV/r plus RAL</td>
<td>2 Years</td>
<td>VL fell from 1,560 to 50 copies/ml; CD4+ T-cell counts rose from 53 to 365 cells/μl</td>
</tr>
<tr>
<td>5</td>
<td>ARV-naive with PR mutation I89V</td>
<td>TDF/FTC plus RAL</td>
<td>2 Years</td>
<td>VL fell from 331 copies/ml to UD; CD4+ T-cell counts rose from 180 to 295 cells/μl</td>
</tr>
</tbody>
</table>
with HIV-1 [3, 4]. The persistence of several different integrase inhibitor mutations among four patients failing HIV-2 salvage therapy in the first, and in one case in the second year after stopping RAL among the series published by Charpentier et al. [5] suggests these mutations have a low fitness cost. These two findings argue against the use of RAL in salvage therapy where, unlike the cases presented here, full viral suppression is no longer a realistic goal of treatment.

RAL appears to perform well in treatment-experienced patients where it can still be paired with other ARVs to which the virus is susceptible. Second-line therapy is potentially important for a large proportion of patients with HIV-2 because their first-line regimens may not have been sufficiently potent [6]. This may come about through the misdiagnosis of HIV-2 as HIV-1, as described elsewhere [1, 7] and seen in our cases for patients 2 and 3. Moreover the key role of boosted protease inhibitors has only recently been demonstrated [1, 8–10], consequently a number of patients currently infected with HIV-2 and under care may have inadequate regimens in their treatment history.

Compared to HIV-1, there is less information to support HIV-2 therapy decisions [11] and a randomized controlled trial of HIV-2 salvage is unlikely to be conducted. Case series with genotypic information will therefore likely remain the best data available for the foreseeable future. While the evidence to date suggests RAL could be an important option for treatment-experienced patients with limited resistance to ARVs, the optimal role of RAL in HIV-2 therapy has yet to be determined. RAL appears to be well tolerated and potent and might have a role in first-line regimens for HIV-2, or as part of a simplification or switch strategy for patients whose first-line regimen includes a boosted PI. To date, these remain untested approaches. As the burden of HIV-2 falls disproportionately on highly resource-constrained settings, the price of RAL, not its characteristics as an antiretroviral medication, will likely determine its place in sequential ARV therapy.

Acknowledgements

The authors would like to acknowledge Phyllis Kanki, and the Laboratoire de Rétrovirologie (CRP Santé) in Luxembourg, for having provided specimens, Bernard Poiesz for making the HIV-2 diagnosis in one of the cases, and Vic Arendt, as treating physician of one of the cases.

Disclosure statement

JR has received a research grant from Merck Sharp & Dohme. All other authors declare no competing interests.

References


