Case report

Ongoing HIV replication in cerebrospinal fluid under successful monotherapy

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We report a case of an HIV-infected patient who was successfully treated with ritonavir/lopinavir (r/LPV) monotherapy for several years. He presented with neurological symptoms and high HIV RNA levels in cerebrospinal fluid (CSF). Sequencing of the HIV from the CSF revealed mutations in the protease gene reflecting resistance against most protease inhibitors, that is, lopinavir and ritonavir. His regimen was switched and after 2 months the HIV RNA viral load was again undetectable in both plasma as well as in CSF. Monotherapy with r/LPV may not be sufficient to fully suppress viral replication in the central nervous system in all individuals and may lead to compartmentalization and the selection of resistant mutations of HIV in the central nervous system.

Introduction

Due to the introduction of HAART, the prognosis of HIV-infected patients has improved gradually. Treatment with HAART has reduced the frequency of opportunistic infections of the central nervous system (CNS) through reconstruction of the immune system [1]. Still, CNS complications are observed in long-term treated subjects [2].

We report a case of an HIV-infected patient presenting with neurological symptoms and high HIV RNA levels in cerebrospinal fluid (CSF) despite successful long-term treatment with monotherapy ritonavir/lopinavir (r/LPV).

Case

A 57-year-old HIV-infected man presented with dysarthria, dysphagia, dyskinesia and tremor. He had been treated with HAART for 12 years. Due to side effects of different regimens he had been ultimately prescribed monotherapy r/LPV 50/200 mg twice daily for the past 9 years. During this time his plasma HIV-1 RNA levels were almost always <400 copies/ml, which is the threshold for detectability (Figure 1 and Table 1).

At presentation he had a CD4+ T-cell count of 930×10^6 cells/l and plasma HIV RNA level of 400 copies/ml. A cerebral magnetic resonance image (MRI) showed changes in white matter suggestive of encephalitis. In his CSF, he had an elevated protein level of 1,140 mg/l and pleocytosis (white blood cells of 25 cells/µl). PCR was negative for cytomegalovirus, Epstein–Barr virus, herpes simplex virus, JC virus, varicella zoster virus, enteroviruses and syphilis. HIV RNA in CSF was 4,500 copies/ml. Lopinavir level 6 h after intake was 0.07 mg/l in CSF and 11.0 mg/l in plasma. This provides a CSF/plasma ratio of 0.6%.

Population sequencing of HIV from the CSF revealed mutations in the protease gene at positions I84V and L10F, reflecting resistance against most protease inhibitors, that is, lopinavir and ritonavir. No mutations were observed in the reverse transcriptase gene. The presence of protease inhibitor resistance mutations could not be confirmed by 454 sequencing, and unfortunately there was insufficient material available to repeat both procedures.

The patient’s regimen was subsequently switched to nevirapine (NVP) 200 mg twice daily and lamivudine/zidovudine 150/300 mg twice daily, and after 2 months the HIV RNA viral load was again undetectable in both plasma as well as in CSF. The CSF sample showed normalization of the cellularity, and his protein level remained high with 915 mg/l with a white blood cell count of 6 cells/µl. The patient’s neurological symptoms improved, however, the MRI of the CNS remained unchanged. Due to side effects on this treatment, NVP was changed to raltegravir.
Discussion

Since the introduction of HAART, the incidence of complications following HIV infection has severely declined. HAART has been shown to have a large effect on restoring the immune function and thereby preventing opportunistic infections [1,3]. Nonetheless, recent literature shows increasing evidence of ongoing viral replication in CNS under HAART, despite successful suppression of plasma viraemia [4,5].

Low penetration of HAART into CSF could lead to incomplete suppression of viral replication in the CNS [4,6,7]. In HIV-infected treatment-experienced adults, the median lopinavir concentration in CSF was 11,200 pg/ml and the median CSF-to-plasma concentration ratio was 0.225%, with concentrations above the median 50% inhibitory concentration for wild-type HIV-1 replication in all patients [6,8]. In our patient, the plasma/CSF ratio was high, at 0.6%. Therefore, in our patient, a low lopinavir concentration in CSF could not readily explain ongoing viral replication.

Few studies have reported detectable HIV RNA in CSF, despite undetectable HIV RNA levels in blood [5,6,9–13]. It has been demonstrated that HIV viral populations vary in different parts of the CNS, suggesting compartmentalization of the HIV infection in the CNS, possibly due to differences in penetration of antiretrovirals [2,9,10,14]. Compartmentalization may
lead to functional differences between virus populations in CSF and blood that may impair antiviral drug susceptibility. Recent studies reported high proportions (10%) of subjects with detectable viral load in the CSF despite low plasma viraemia [4,5].

Ongoing replication and changes in white matter in our patient, despite adequate LPV/r levels in CSF, suggest poor penetration of LPV/r in the CNS. Data on penetration of lopinavir and other antiretrovirals in these compartments are lacking. It is suggested that monotherapy with r/LPV may result in more failure in CNS than combination therapy [14]. Gutmann et al. [14] reported that r/LPV monotherapy is not recommended, since 6 of the 60 patients demonstrated viral failure in blood. Among the failing patients, five patients with lumbar puncture also had an elevated HIV RNA load in CSF [7,15]. Nonetheless it has also been demonstrated that CSF viral replication may also occur during treatment with HAART [5].

Suppression of HIV replication and clinical improvement after switch of regimens suggests a better penetration in CNS of nucleoside reverse transcriptase inhibitors and or non-nucleoside reverse transcriptase inhibitors in our patient. This might explain the incomplete suppression of viral replication in CNS in our patient and the resulting viral mutation and resistance to r/LPV and consequently a detectable HIV RNA in his CSF.

Conclusions

Despite a long-standing suppression of viral replication in plasma, we found substantial viral replication in the CSF despite adequate r/LPV levels in CSF. Our observation supports the suggestion from recent literature that monotherapy with r/LPV may not be sufficient to fully suppress viral replication in the CNS in all individuals and may lead to compartmentalization and the selection of resistant mutations of HIV in the CNS. Since this phenomenon is also described in patients receiving HAART, we strongly suggest physicians to be more aware of possible CNS disorders due to CSF viral replication, despite successful treatment.

Disclosure statement

All authors declare no competing interests.

References


