Ritonavir boosted indinavir treatment as a simplified maintenance 'mono'-therapy for HIV infection

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Triple combination is currently the fundamental concept for HIV therapy. We evaluated the feasibility of a 48-week maintenance therapy with ritonavir-boosted indinavir in 12 HIV-infected patients. All patients maintained viral suppression (< 50 copies/ml) throughout the study (one drop-out after week 32) and opted to continue on this monotherapy thereafter. At week 48, no changes in fat distribution patterns were detectable using a dual-energy X-ray absorptiometry scan. These results support the further evaluation of mono-maintenance trials.

Since the introduction of protease inhibitors (PI) in HIV treatment, highly active antiretroviral therapy (HAART) is usually given as a combination of three drugs. In the past few years, long-term side effects, particularly mitochondrial toxicity of nucleotide reverse transcriptase inhibitors (NRTI), were recognized as a cumulative risk for patients on long-term HAART.

One potential approach to lower the potential side-effects could be to reduce the number of drugs after initial induction with HAART. Previous attempts to switch to indinavir monotherapy after induction with a three-drug regimen failed [1]. However, the high inhibitory quotient of currently used ritonavir-boosted PI make these compounds potential candidates for efficient mono-maintenance therapy [2]. If effective, such a simplified treatment would not only limit side-effects but also reduce costs and result in more acceptable treatment regimens with improved adherence.

We conducted a pilot study to evaluate the potential of ritonavir-boosted indinavir monotherapy to maintain HIV-RNA suppression. Ritonavir-boosted indinavir was selected for its superiority to reach the cerebro-

spinal fluid and genital compartments [3,4]. Trough levels of indinavir are several-fold higher than the IC_{95} of wild-type HIV [5]. In addition, biological markers were evaluated to be used in a continuation study.

Patients on ritonavir-boosted indinavir-based HAART (with two NRTI) were eligible for the study if their blood HIV-RNA level was less than 50 copies/ml for at least 3 months and no previous treatment failure was documented. The study was approved by the local ethical commission and written informed consent was obtained. All participants were offered comprehensive adherence support including medication event monitoring system caps. The dose of indinavir was adapted to achieve trough levels of 500–2000 nM/l (400 mg twice a day, n = 1; 600 mg twice a day, n = 4; 800 mg twice a day, n = 7). At baseline, all NRTI were stopped and only ritonavir-boosted indinavir maintenance therapy was continued.

HIV-RNA levels were measured every 4 weeks by ultrasensitive HIV-RNA polymerase chain reaction [6] (detection limit < 20 copies/ml) throughout the 48-week study period. The primary endpoint was a treatment failure defined as one confirmed HIV-RNA level greater than 400 copies/ml or three consecutive HIV-RNA blood values greater than 200 copies/ml. The pre-defined stopping criteria for the study was the occurrence of treatment failure in two out of 12 patients.

In an attempt to evaluate additional parameters to be included in a large-scale follow-up study, additional information on CD8 cell activation markers, HIV-RNA levels in semen and mitochondrial toxicity in semen and peripheral blood mononuclear cells were obtained (results not shown). The hip-to-waist ratio and body fat distribution pattern (dual-energy X-ray absorptiometry scan) were examined at baseline and week 48. Additional biological markers were obtained but are not reported here (CD4 cell activation markers, mitochondrial DNA contents in peripheral blood mononuclear cells and sperm).

Twelve patients (11 men) were included. The median duration of HAART was 28.5 months (minimum 5, maximum 65). The previous NRTI regimens were zidovudine/lamivudine (n = 9), stavudine/lamivudine (n = 1), stavudine/didanosine (n = 1), abacavir/lamivudine (n = 1). The median HIV-RNA level and CD4 cell count before HAART was 5.1 $\log_{10}$ (3.6–6.6) copies/ml and 190 cells/μl, respectively.

Four subjects experienced nephrotoxicity, with three events of urolithiasis and increasing creatinine levels in two. One patient developed primary central nervous system T-cell lymphoma (during study week 24). His HIV-RNA level remained less than 20 copies/ml throughout the study and his CD4 cell count was always greater than 650 cells/μl (> 26%). The patient opted to continue on ritonavir-boosted indinavir monotherapy and was started on chemotherapy for his lymphoma. At approximately week 32, the patient committed assisted suicide.

All the other patients remained in the study for the planned 48 weeks and no patient reached a predefined primary endpoint. The HIV-RNA blood level measurements showed variable dynamics with short-term viral load increases greater than 200 copies/ml (n = 1), 100–200 copies/ml (n = 3), and 50–100 copies/ml (n = 7). The vast majority (113 RNA measurements) remained below 25 copies/ml. The number of HIV-RNA blips above 100 copies/ml (four in 144, 3%) was in the same range as in our average HIV-infected clinic patients with long-term HIV-RNA suppression (132 blips > 100 in 2437 HIV-RNA determinations, 5%). Three out of four blips greater than 100 copies/ml occurred in one subject. As shown in Fig. 1, the frequency of viral load blips decreased over time. After completion of the study at week 48, all 11 patients opted to remain on the study treatment and remained suppressed for a median of 78 weeks at the time of manuscript submission. No further blip above 100 copies/ml was observed.

The prevailing strategy to treat HIV infection with three drugs is based on the pharmacokinetics of PI achieving trough levels slightly above the IC_{95} of wild-type HIV. Boosting antiviral drug levels by the inhibition of drug metabolism with low-dose ritonavir is currently a favourite method to increase the efficacy of PI-based HAART. Theoretically, if all body compartments can be reached with such a high drug level, one active drug might suffice to suppress the viral load [3]. To our knowledge, the use of only one highly dosed PI has never been prospectively evaluated.

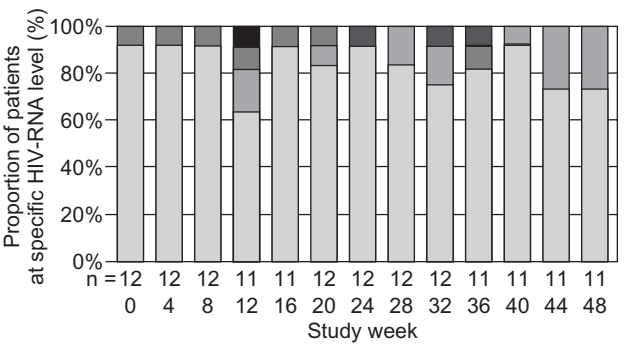

Fig. 1. Level of HIV suppression during the study. At each study site visit the frequency of patients with the specified level of HIV-RNA results is given: HIV-RNA < 25 copies/ml ▫ 25–50 copies/ml ▪ 50–100 copies/ml ▪; 100–200 copies/ml ■ 200–400 copies/ml ■.

In this pilot study, treatment with only one antiviral compound (boosted with low-dose ritonavir) effectively maintained the blood viral load to levels below 50 copies/ml for a median time of 78 weeks in patients who have previously been on a successful HAART therapy. However, these results should not lead to an uncontrolled use of ritonavir-boosted PI monotherapies. Some important features of this pilot study need to be emphasized: First, this study was performed in selected patients who had successfully suppressed their HIV-RNA load. Chances to develop antiviral resistance are markedly reduced in patients with fully suppressed HIV RNA. Second, we selected a PI with an excellent record of cerebrospinal fluid/genital tract penetration to limit the chances of resistance selection in these sanctuaries [7]. Third, special efforts were made to increase drug adherence (including medication event monitoring system cap feed-back) and therapeutic drug monitoring was performed to reduce the risk of drug toxicity.

The occurrence of a central nervous system T-cell lymphoma in a patient with a high CD4 cell count is an unusual event. This event is unlikely to be a consequence of simplified treatment, given the excellent HIV-RNA suppression and high CD4 cell count.

The number of low-level HIV-RNA blips observed in this small population with monthly HIV-RNA determinations requires attention. Among 144 HIV-RNA measurements, the vast majority (113) was below the highly sensitive HIV-RNA detection level of 25 copies/ml. Notably, the frequency of blips at a given timepoint and the number of activated CD8+CD38+ cells did not increase over time (not shown).

In summary, this pilot study supports the further investigation of ritonavir-boosted PI mono-maintenance treatment in larger populations. This treatment strategy has a potential to limit the costs and adverse events related to NRTI.

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