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title

Is Ritonavir-boosted Protease Inhibitors (PIs/r) monotherapy noninferior to classic combined antiretroviral therapy (cART)?

authors

Tomasz Mikuła • Magdalena Dąbrowska • Alicja Wiercińska-Drapało

Department of Hepatology and Acquired Immunodeficiences,
Warsaw Medical University, Poland

summary

The idea of boosted protease inhibitor (PI) monotherapy was created as investigational treatment and simplification strategy in patients with virologic suppression on cART, especially to enhance lifelong adherence. Moreover, it has been considered that elimination of nucleoside reverse transcriptase inhibitors (NRTIs) from an antiretroviral (ARV) regimen might reduce cost of treatment and potentially decrease its toxicity, particularly long-term adverse effects as lipodystrophy or cardiovascular complications, and the risk of HIV multidrug resistance. In 2009, LPV/r and DRV/r monotherapy has been started to recommend by European AIDS Clinical Society (EACS) as a new optional therapeutic strategy for HIV-infected treatment-experienced patients, however only for persons without history of failure on prior PI-based therapy and with undetectable viral load (< 50 cp/mL) for at least 6 months.

The main purpose of this paper was to give an overview of all ritonavir-boosted PI (PI/r) monotherapy studies published in peer-reviewed medical journals or presented at international HIV conferences and assess its efficacy in comparison to the traditional cART.

key words

HIV infection, cART, protease inhibitors (PIs/r), monotherapy

address

Dr Tomasz Mikuła
Department of Hepatology and Acquired Immunodeficiences
Warsaw Medical University
01-201 Warsaw, 37 Wolska Street, Poland
e-mail: mikula@zakazny.pl

INTRODUCTION

The idea of boosted protease inhibitor (PI) monotherapy was created as investigational treatment and simplification strategy in patients with virologic suppression on cART, especially to enhance lifelong adherence. Moreover, it has been considered that elimination of nucleoside reverse transcriptase inhibitors (NRTIs) from an antiretroviral (ARV) regimen might reduce cost of treatment and potentially decrease its toxicity, particularly long-term adverse effects as lipodystrophy or cardiovascular complications, and the risk of HIV multidrug resistance.

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LOPINAVIR/RITONAVIR MONOTHERAPY

Lopinavir/ritonavir (LPV/r) was the first boosted PI analyzed from the monotherapy point of view. In 2003, at 9th European AIDS Conference in Warsaw, one of the first data suggesting the efficacy of the switch to LPV/r monotherapy after initially achieved HIV viral suppression on cART was presented (1). Then, similar results from OK Study were showed at XV International AIDS Conference in Bangkok, Thailand in 2004 (2). Moreover, at the same conference, the results of the study including 30 HIV-infected naïve-patients on LPV/r monotherapy were reported. After 48 weeks of LPV/r monotherapy dosing by body weight (400/100 mg bid < 70 kg and 533/133 mg bid > 70 kg), 18 (60%) patients had HIV RNA < 50 cp/mL (3).

In 2006, the several studies on LPV/r monotherapy efficacy were presented at the XVI International AIDS Conference in Toronto, Canada. Firstly, Bill Cameron from the University of Ottawa presented results of M03-613 study. It was a 2-year randomized controlled clinical trial in 155 naïve-antiretroviral HIV-infected patients who firstly obtained LPV/r and CBV (Combivir®) induction followed by LPV/r monotherapy maintenance after negative viral loads (VL) for 3 months or combination of efavirenz (EFV) and CBV. The study showed that subjects in LPV/r monotherapy arm had more HIV VL 'blips' between 50 and 500 cp/mL compared with those on EFV arm. Moreover, the final results demonstrated the greater efficacy of EFV/CBV therapy: 91% patients presented VL < 50 cp/mL and 95% < 500 cp/mL (95%) vs 62% and 84% on LPV/r monotherapy (4). In 48-week MONARK study, Jean-Francois Delfraissy from the Kremlin Bicêtre Hospital in Paris, randomised 136 treatment-naïve patients to initial LPV/r monotherapy arm (n=83) or LPV/r plus AZT/3TC arm (n=53). At baseline, VL was less than or equal to 100,000 copies/mL and CD4 was greater or equal to 100 cells/mL. The final results from 48 week showed that only 84% of patients on LPV/r monotherapy had VL < 50 copies/mL vs 98% on cART. Moreover, the 'blips' were more often observed in LPV/r monotherapy arm in comparison to cART arm. Total CD4 cell count was similar between two studied groups, however protease-associated mutations occurred more frequently in the LPV/r monotherapy group (2/83) then in the cART group (single RT mutation M184V) (5). In contrast to the MONARK study, the Spanish OK04 study has been focused on LPV/r monotherapy efficacy in patients previously treated with LPV/r plus 2NRTIS therapy and with VL < 50 cp/mL for > 6 months, and no history of virological failure on a PI. One hundred ninety eight subjects were randomized: 100 for LPV/r monotherapy and 98 for cART (LPV/r + 2NRTIs). After 48 weeks, the percentage of patients with HIV RNA < 50 cp/mL was 94% in the monotherapy group and 90% in the triple therapy group on treatment analysis and 89% vs 90% on intention-to-treat analysis, respectively (6). In the Kaletra Monotherapy (KALMO) study, Nunes et al. examined 60 Brazilian patients who were randomized to LPV/r monotherapy arm or to cART arm after at least 6 months of successful cART. At 96 weeks, 80% vs 89.7% had HIV-RNA < 80 cp/mL (7). Waters L. and colleagues from the Chelsea and Westminster Hospital in London observed 35 treatment-experienced patients previously using LPV/r with low adherence to cART in anamnesis. Fifty percent (14/28) patients on LPV/r monotherapy achieved VL < 50 cp/mL and 73% at least > 1 log VL reduction. Unfortunately, 8 from them had to switch therapy (3 due to virological failure, 1 due to immunological failure, 2 due to 'blips', and 2 due to unclear reasons), but the rest continued LPV/r monotherapy. Finally, 12/20 had undetectable VL after 13.5 months of observation (8). The ineffectiveness of once daily dosed vs twice daily dosed LPV/r monotherapy was showed by Falci et al. among treatment-experienced patients with VL < 50 cp/mL for the previous 6 months (9). Martin et al. from Mortimer Market Centre in London presented retrospective results of 13 patients using monotherapy with LPV/r (n=13) or ATV/r (n=3). Median CD4 was 190 cells/mL and VL – 5100 cp/mL. Unexpectedly, at the start of the monotherapy only 4/16 patients had VL < 50 cp/mL but after 12 week of PIs monotherapy 7/14 (50%) and 9/14 (64%) achieved virological suppression < 50 cp/mL or < 400 cp/mL, respectively (10).

In 2007, at 4th IAS Conference in Sydney, Australia, Gathe et al. presented the second part of IMANI study. It was IMANI-2 results of 39 cART-naive patients treated with LPV/r monotherapy. After 48 weeks, 31/39 (79.5%) patients had HIV VL < 75 cp/mL. However, six of them had problems with good adherence, two developed new minor PI mutations and one patient a major PI mutation (11).

In 2009, at 12th European AIDS Conference/EACS in Cologne, Germany the 1-year study performed among patients from Argentina, Mexico and Canada was presented. All included subjects (n=80) had been obtained PI-based cART and 56% were on LPV/r. Generally, 9 ARV therapy discontinuations was observed: 7 in cART arm and 2 in monotherapy arm. Four patients had VL 'blips' and were successfully re-suppressed. Only 2 patients – one in each group – had a virological failure. On an intent-to-treat analysis 30 patients (93.8%) in the standard therapy and 37 (94.9%) in the monotherapy had undetectable HIV-1 RNA VL at week 48. The enhanced level of LDL-cholesterol was observed in 71% patients on LPV/r monotherapy in comparison to 44% on standard therapy (12). Moreover, the third part of IMANI – IMANI 3 study was also presented. Four patients from IMANI 1 were included to IMANI 3 study and as a result they had already been on successful LPV/r monotherapy for 6 years. The main goal of IMANI 3 study was to assess LPV/r monotherapy efficacy in patients taking LPV/r in the new Meltrex® formulation tablets dosed once