Monotherapy in HIV-1-Infected Adults: An Update

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Abstract

Development of drugs treating HIV-1 infection and the unquestionable efficacy of antiretroviral therapy highlights the need for less toxic and cheaper regimens that could simplify the treatment of this infection without sacrificing efficacy. The favorable pharmacokinetic profile of boosted protease inhibitors, together with the multi-mutations that HIV-1 need to operate in its genome to become resistant to this class of drugs, make them ideal candidates for the use in monotherapy. Results available from clinical studies, especially with lopinavir/ritonavir (Kaletra®) as well as darunavir (Prezista®) boosted ritonavir showed a real virological and clinical outcome compared to standard antiretroviral therapy. In addition, the first showed to have a good penetration in the cerebrospinal fluid, while the second in the seminal fluid. However, particular attention need to take into account for the potential consequences of viral replication in sites where the penetration of protease inhibitors may be poor, e.g. sanctuary reservoir, thus before this strategy can be considered for routine use this concern needs to be deeply investigated.

ABBREVIATIONS

ART: Anti-Retroviral Therapy; HAART: Highly Active Antiretroviral Therapy; NRTIs: Nucleos(t)ide Reverse Transcriptase Inhibitors; NNRTIs: Non Nucleoside Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; VF: Viral failure; MT: Monotherapy; RCT: Randomized Controlled Trial

INTRODUCTION

The pharmacological history of AIDS began in 1987 when zidovudine (AZT; a NRTI) became the first approved drug for the treatment of patients with HIV-induced immunodeficiency at early and advanced stage of the disease. Afterwards, other NRTIs were approved for clinical use. In 1995, the effect of a new class of drugs, PIs on the prognosis of patients with advanced HIV-1 disease yielded to profound changes in the therapeutic management of AIDS. A third class of antiretroviral drugs, the NNRTIs, became available in 1998. At the same time data from clinical trials along with the better understanding of HIV-1 biology and of drug-resistance mechanisms led to triple-drug combination therapy based on at least 3 antiretroviral drugs including 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus 1 boosted protease inhibitors (Pis) or plus 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) (from few years alternatively also 1 integrase inhibitor) [1–3]. This pharmacological approach is known as highly active antiretroviral therapy (HAART). Combination antiretroviral therapy dramatically suppresses viral replication and reduces the plasma HIV-1 viral load to below the limits of detection to the most sensitive clinical assay (<50 RNA copies/mL), usually resulting in a significant reconstitution of the immune system as measured by an increase in circulating CD4+ T-lymphocytes level [1–3].

The introduction and the widespread use of HAART dramatically changed the perspective of HIV-1 infection, form an acute life-threatening disease to a disease that can, with timely and effective treatment, be managed as a chronic condition. High adherence to HAART is critical for treatment success and to avoid the development of drug resistance. In this concern, monotherapy with boosted PIs is particularly attractive as an NRTI-sparing strategy. PIs monotherapy could improve the adherence, decrease costs, and preserve future treatment options [4,5]. However, guidelines consider this approach only in cases of NRTI-related toxicity or intolerance [6]. Increasing evidence in clinical data and in routine clinical practice, showed that lopinavir/ritonavir (LPV/r) monotherapy seems to be effective similarly to the triple HAART standard therapy, in the maintenance of virological suppression even when re-suppression of HIV-1 RNA is due to the reintroduction of NRTIs [7,8]. LPV/r monotherapy has been investigated in antiretroviral-naive patients in the randomized MONARK (Monotherapy Antiretroviral Kaletra) trial [9] and other four randomized trials (OK, OK-04, M03-613 and the KalMo studies) [7,8,10,11]. One concern about boosted-PI monotherapy is its ability to control HIV-1 replication in sanctuary anatomical reservoirs such as the male genital tract and the central nervous system. However, recently it was reported that monotherapy...
with LPV/r can successfully controls the viral replication also in cerebrospinal fluid (CSF) [13].

**PROTEASE INHIBITORS**

Ten PIs are currently approved by FDA are amprenavir (APV, Agenerase), atazanavir (ATZ, Reyataz), darunavir (TMC114, Prezista), fosamprenavir (Lexiva), indinavir (IDV, Crixivan), lopinavir (LPV), nelfinavir (NFV, Viracept), ritonavir (RTV, Norvir), saquinavir (SQV, Fortovase/ Invirase), tipranavir (TPV, Aptivus) and lopinavir/ritonavir (LPV/r,Kaletra), darunavir/ritonavir(DVR/r Prezista). All PIs share relatively similar chemical structures and cross resistance is commonly observed (Figure 1).

The HIV-1 protease is the enzyme responsible for the cleavage of the viral gag and gag-pol polyprotein precursors during virion maturation [14]. The enzyme is constituted by 3 chains A, B and C. The site of action of PIs is localized in the C chain where this class of drugs interacts with the specific aminoacid sequences X-Ser-Leu-Asn-X-Ile-X. Because of its vital role in the life cycle of HIV-1 and relatively small size (11 kDa), it was initially expected that resistance to protease inhibitors would be rare. However, the protease gene has great plasticity, with polymorphisms observed in 49 of the 99 codons, and more than 20 substitutions known to be associated with resistance [15]. In PIs drugs resistance, HIV-1 seems to follow a stepwise pathway to overcome drug selection: i) acquisition of primary resistance mutations in the protease gene, ii) selection of secondary/compensatory protease mutations to repair the enzymatic function and rescue viral fitness, and iii) selection of mutations in the major cleavage sites of the gag and gag-pol polyprotein precursors that restore protein processing and increase production of the HIV-1 protease itself [16-21]. The combo drug LPV/r rare commercially available and their boosting leads to a favorable pharmacokinetic profile that, coupled with the simple dosing scheme, are associated with a low risk of treatment failure for reaching of optimal blood concentration levels. The co-formulation, from few years approved for clinical use in tablets (before was in soft-gel capsules) and in liquid form is taken twice-daily; it is also approved for once-daily for treatment-naive adults. One of the main advantages using them as monotherapy is that patients cannot fail to take one component of the regimen due to the co-formulation. Taking either the active PIs or ritonavir alone, without this latter may increase the risk of viral rebound and PIs resistance due to inadequate concentrations to maintain viral suppression.

**MONOTHERAPY STUDIES**

In the last 10 years, several studies of boosted PIs monotherapy were conducted in suppressed and unsuppressed HIV-1-RNA patients. In 2004 Kahlert [4] et al. published the results of an uncontrolled trial with Indinavir/ritonavir (IDV/r) monotherapy in patients suppressed IDV/r based HAART. The switching from HAART to IDV/r monotherapy lasting 48 weeks and during these period virologic failures occurred. A similar study was conducted in 2005 by Ebrahim and Hill [21], using saquinavir (SQV)/r monotherapy in 28 unsuppressed

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**Figure 1**: Protease inhibitors and the crystal structure of HIV-1 protease complexed with ritonavir (Protein Data Bank extract: http://www.rcsb.org/pdb/home/home.do).
patients with advanced HIV-1 infection. The study highlights virologic and immunologic response similar to SQV/r based HAART. Successively, Swindells [5] et al. in 2006, Vernazza et al and Karlstrom et al, both in 2007 [23-24] in three different uncontrolled clinical trials evaluated the efficacy of Atazanavir (ATV)/r monotherapy in suppressed patients. In the first study, about 85% of patients earlier showed virologic failure, similar to the second, where in the 7% of patients ATV/r monotherapy, failed. The third ones were interrupted after an early virologic failure in five patients out of 15 (counting the 30%). The combo drug Lopinavir/-r (LPV/r) as monotherapy are the PIs molecules more studied in clinical trials. (LPV/r), at the moment is the solely PIs studied in a controlled clinical trials. The only Randomized Clinical Trialon LPV/r monotherapy in naïve HAART patients has been conducted by Delaugere et al. in Europe called MONARK (Monotherapy Antiretroviral Kaletra) study [9]. MONARK trial compared LPV/r monotherapy (herein indicate as group A) with LPV/r associated with zidovudine/lamivudine (Combivir) (herein indicate as group B). The study enrolled 138 randomized patients: 84 in the group A and 54 in the group B. The first end-point at 24 weeks of follow up showed no significant differences between the two groups in the rates of virologic suppression (<400 copies/ml). However, at the second end-point (48 weeks) a larger proportion of patients in group B had viral loads of <50 copies (98versus 84%; p = 0.03). LPV/r has been evaluated in at least others four maintenance trials known as OK, OK 04, M03-613 and the KalMo studies, comparing monotherapy with standard triple therapy, after viral suppression [7,8,10-12]. These studies had much better results than MONARK ones, since they were carried out on patients previously virologically suppressed. For example, the OK04 study demonstrated that subjects who experienced virologic suppression while receiving lopinavir/ritonavir and 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and whose treatment then was simplified to lopinavir/ritonavir monotherapy maintained virologic suppression at rates similar to those in subjects who continued the triple combination therapy (85% vs. 90%, respectively, for the proportion of subjects maintaining HIV-1 RNA at <50 copies/mL; P=0.31) through 48 weeks [7]. Through 96 weeks, percentage of patient without therapeutic failure was 87% (monotherapy, n = 100) vs. 78% (triple therapy, n = 98). Percentage with HIV RNA, <50 copies per milliliter (intention to treat, missing = failure, re-induction = failure): 77% (monotherapy) vs.78% (triple therapy). Low-level viral rebound was more frequent in the monotherapy group. Twelve patients in the monotherapy group (12%) needed reinduction with nucleosides. Discontinuations due to adverse events were significantly more frequent in the triple therapy group (8%) than in the monotherapy group (0%); P = 0.003 [8].

The last PIs approved by US FDA is DRV/r (Prezista formerly known as TMC114), was used in further two randomized clinical trials, called MONET and MONOI [25,26]. In the first trial, 256 patients with HIV-1 RNA, <50 copies/mL on current anti-retrovirals were switched to DRV/ronce daily, either as monotherapy (n=127) or with two nucleoside analogues (n=129). Treatment failure was defined as two consecutive HIV-1 RNA levels at least 50 copies/mL by week 96, or discontinuation of study drugs. The trial had 80% power to show non-inferiority at week 48 [25]. In the efficacy analysis, HIV-1 RNA, <50 copies/mL by week 96 was 78% versus 82% in the monotherapy and triple therapy arms; in a switch included analysis, HIV-1 RNA <50 copies/mL was 93% versus 92%. The percentage of patients with HIV-1 RNA <50 copies/mL (optical density from the sample equal to the negative control) remained constant over time in both treatment arms [25].

MONOI is a prospective, open-label, non-inferiority, randomized, 96 weeks trial comparing DRV/r monotherapy versus a DRV/r triple-therapy strategy to maintain HIV-1 viral load suppression [26].

From 225 randomized patients, 219 patients reached the 48 weeks follow-up and 211 reached the 96 weeks follow-up (106 patients in the DRV/r monotherapy arm and 105 in the DRV/r triple-therapy arm). At week 96, in intent to-treat analysis, 91/103 patients (88%) allocated to the DRV/r monotherapy arm and 87/104 patients (84%) allocated to the DRV/r triple-therapy arm achieved an HIV-1 viral load <50 copies/mL, with no statistical difference between the two groups. Throughout the 96 week follow-up, 66/112 patients (59%) and 79/113 patients (70%) consistently had HIV-1 RNA, <50 copies/mL with DRV/r monotherapy and DRV/r triple therapy, respectively [25].

**DISCUSSION AND CONCLUSION**

Studies evaluating boosted of protease inhibitors monotherapy have been performed in three different clinical settings: i) initial treatment; ii) induction-maintenance; iii) simplification monotherapy in patients having virological suppression (patients without prior virological failure).

The rationale applied in those clinical trials was to avoid NRTIs toxicity and to decrease national health costs, taking also advantage of the high barrier to resistance of boosted PIs. Although several studies have been published, this therapeutic approach still is not recommended in the US and the UK [27]. Recently introduced the concept of “Less Drug Regimens” in the European guidelines and Italian licensing authority have allowed this therapeutic strategy in 2013 and only in selected patients [28,29]. However, debate remains opened if the monotherapy is a safe and effective. In addition, there is an important concern about the ability of monotherapy to penetrate viral reservoirs and prevent viral replication in sanctuary sites, such as genital tract and central nervous system [30]. The studies commented in this paper shown that boosted PIs monotherapy has a similar efficacy to standard triple-drug therapy (despite in the monotherapies study on LVD/r were used soft-gel formulation, less tolerated than new formulation tablets). The studies commented in this paper shown that boosted PIs monotherapy has a similar efficacy to standard triple-drug therapy (despite in the monotherapies study on LVD/r were used soft-gel formulation, less tolerated than new formulation tablets). However rebound viremia, which is typically very low, is more common observed with monotherapy than triple therapy and patients who fail the monotherapy strategy can be re-suppressed again by adding nucleosides or switching to a triple therapy regimen. In this concern, in order to overcome these limitations, PROTEA study recently presented at the international AIDS meeting in Glasgow 2014, as well as the GARDEL study highlights that when boosted PI are associated with lamivudine the achievement of the correct
control of viremia is better [31]. The challenge for the future is designing studies that should be conducted with strict selection criteria such as long-lasting undetectable HIV-1 RNA copy levels (1 year or more), no history of PIs failure, CD4+ T-lymphocytes good levels at switch (400/µL or more), no HBV co-infection, high adherence to HAART and especially very low levels of HIV-1 DNA.

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REFERENCES


