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One Year Follow-Up of Darunavir/Cobicistat Monotherapy in Pretreated HIV Patients

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Abstract

Introduction: Boosted protease inhibitor monotherapy (PI/r): Darunavir/ritonavir (DRV/r) or Lopinavir/ritonavir (LPV/r) monotherapy is only provided in the major treatment guidelines in pre-treated HIV patients to prevent toxicity associated with nucleoside/nucleotide reverse transcriptase inhibitor (NRTIs), reduce costs and simplify antiretroviral treatment. To start PI/r monotherapy, according to GESIDA guidelines 2016, patients need to meet the following criteria: absence of chronic hepatitis B, plasma viral load <50 copies/ mL for at least 6 months and absence protease inhibitors mutations or previous virologic failures to PI/r. Currently, there are no studies that evaluate the efficacy and safety of DRV/COBI monotherapy.

Methods: This prospective study analyzed pretreated HIV patients with DRV/r monotherapy that were switched to DRV/COBI monotherapy. The aim of the study is to describe the effectiveness and safety of the DRV/COBI monotherapy.

Results: A total of 78 patients were evaluated. In total 11.53% (9/78) patients developed "blips" (Plasma viral load: 50-200 copies/ml) in our study and four patients had a viral load ≥ 200 copies/mL. Twelve patients (15.38%) switched to another antiretroviral treatment, so at week 48 only 66 of the 78 patients continued with DRV/COBI monotherapy. Three patients continued with "blips" at week 48. Despite "blips", virological rebounds and switch in treatments, 95.45% (63/66) of the patients with DRV/COBI monotherapy were maintained with a viral load <37 copies/mL at week 48 of the follow-up. In addition, there had been a slight increase in the CD4+ T cell count at week 48 of follow up. As for safety, there were no significant differences in lipid profile, liver function (transaminases) and renal function between DRV/r and DRV/COBI monotherapy.

Conclusions: DRV/COBI monotherapy seems to be effective and safe (lipid profile, liver and kidney function). However, it will be necessary to design specific studies comparing DRV/r vs DRV/COBI monotherapy to confirm these results.

Keywords: Ritonavir-boosted protease inhibitor monotherapy; Darunavir/ritonavir; Darunavir/cobicistat

Introduction

The availability of antiretroviral treatment (ART) has made it possible to consider HIV-1 infection as a chronic disease. This has led to a change in the objectives of ART with a greater importance in improving the patient's quality of life and more efficient use of the resources, without compromising the effectiveness of treatments. In ART naive patients, on the first and successive lines after ART failure, preferred regimens remain the combination of three active drugs against HIV: Two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir), integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1-3].

Currently, boosted protease inhibitor monotherapy (PI/r): Darunavir/ritonavir (DRV/r) or Lopinavir/ritonavir (LPV/r) is only contemplated in the main treatment guidelines in pretreated patients to avoid toxicity associated with NRTIs, reduce costs and simplify ART. PI/r monotherapy with Atazanavir/ritonavir (ATV/r) is not recommended because of the worst results obtained in clinical trials. To initiate monotherapy based on PI/r, the patient must meet the following criteria: absence of chronic hepatitis B, plasma HIV-RNA viral load <50 copies/mL for at least 6 months and absence of mutations in the protease gene or virological failures (VF) prior to PI/r. PI/r are drugs that have a high genetic barrier and are used in monotherapy to maintain virological suppression in most patients, but with lower rates than triple therapy. The use of monotherapy with Lopinavir/ritonavir (LPV/r) and Darunavir/ritonavir (DRV/r) is associated with a higher frequency of "blips", defined as isolated and transient viral load values between 50 and <200 copies/mL. The "blips", although in most studies are not related to the increased risk of virological failure, do recommend re-evaluation of ART (degree of adhesion and genetic barrier) and in some patients may select resistant mutants [1]. Virological failure occurs when, in a patient with strict adherence and optimal tolerability to ART, there are any of the following two situations: a) Viral load detectable after 24 weeks of initiation of ART; B) if after reaching undetectability, the viral load returns to >50 copies/mL in two consecutive determinations (separated by 2-4 weeks), excluding intercurrent vaccinations or infections (they may produce transient elevations of viral load). Virological failure is

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generally resolved by the reintroduction of 2 NRTIs. The factors that predict success of protease inhibitor monotherapy are high adherence, prolonged and profound virological suppression and CD4 T cell count >100 cells/μL [1]. Actually, there are no available clinical trials comparing the efficacy of a monotherapy between different PI/r.

The currently available boosted agents, ritonavir (RTV) and Cobicistat (COBI), inhibit CYP3A-mediated metabolism which increases the systemic exposure of most PIs and, in the case of COBI, also Elvitegravir (EVG), an INSTI used for treatment of HIV2. Although IP have a high genetic barrier and a good tolerability and safety profile, RTV is associated with gastrointestinal adverse effects, numerous interactions with other drugs, insulin resistance, lipoatrophy and hyperlipidemia [4,5]. Different studies have evaluated the efficacy of DRV/r once daily in combination with other ART (ARTEMIS [6] study in naive patients and ODIN [7] study in pretreated patients) or monotherapy in pretreated patients (MONET, MONOI, Monarch and PROTEA studies) [8-11].

COBI has demonstrated in phase III trials non-inferiority and bioequivalence with respect to RTV, as well as a good tolerance. COBI is associated with lower lipid alterations and less interactions with other drugs, although more studies are necessary to prove this. Unlike RTV, COBI does not have antiretroviral activity, so the appearance of resistance to treatment is not a possible problem [5]. On the other hand, it has to be considered that COBI can decrease estimated glomerular filtration rate (GFR) and increase creatinine levels, attributable to an inhibition of tubular secretion, without altering renal function [4,5].

The authorization of the fixed dose combination of Darunavir/cobicistat (DRV/COBI) 800/150 mg is mainly based on the results of the study GS-US-216-130 [12]. The study evaluates the efficacy and safety of the components separately, mainly in "naive" patients who were given as starting ART regimen: DRV/COBI+2 NRTIs which was equivalent in virological efficacy compared to the ARTEMIS [6] and ODIN [7] studies. In a Phase III study was evaluated the degree of satisfaction of patients on COBI-containing co-formulations versus RTV, as well as the incidence of gastrointestinal side effects. There was an increase in satisfaction and a decrease in gastrointestinal intolerance from week 4 of treatment [13].

In published studies comparing the safety and effectiveness of DRV/COBI or EVG/COBI, patients were treated with a triple therapy with two NRTIs following the recommendations of the current ART guidelines [12,14].

There are currently no available studies which compare the effectiveness of DRV/COBI monotherapy (either alone or in coformulation) with other ART, but its use in selected patients has been proposed as an alternative to avoid long-term comorbidities related to the ART, improve patient satisfaction and increase adherence, directly affecting the effectiveness of treatments and decreasing the occurrence of resistance [6].

The aim of this study is to describe the effectiveness and safety of DRV/COBI monotherapy in HIV pretreated patients in a third level hospital.

Methods

Patient selection and data search

Observational prospective study carried out in a third level hospital. Inclusion criteria: all HIV pretreated patients (≥ 18 years) in treatment with DRV/r monotherapy and who switched to a DRV/COBI monotherapy regimen. Patients should have been at least 24 weeks on treatment with DRV/r monotherapy before the switch. Inclusion period: September 2015 to November 2015 inclusive. Follow-up period: September 2015 to December 2016. Exclusion criteria: Patients from whom adequate clinical and/or analytical information was not available for further analysis and those who did not have an immediately prior treatment line with DRV/r monotherapy were excluded from the study.

The information was obtained from the Hospital's Infectious Diseases service database: AdvanCed HIV 2009, electronic medical records and dispensing records from outpatient software (Cafydim® and APD-Prisma®) Pharmacy Service (Variables collected; Demographic variables: age and sex and Clinical variables: To distinguish).

Treatment with DRV/r

- DRV/r treatment weeks prior to switch.
- Number of different ART lines and schemes used prior to switch with DRV/r
- Virological response: Plasma HIV-RNA viral load (copies/mL) just before the switch.
- Immune response: flow cytometric counts of CD4+ T cells (cells/μL) just before the switch.
- Lipid profile (cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), transaminases hepatic levels: aspartate aminotranserase (AST) and alanine transaminase (ALT) and renal profile (creatinine and glomerular filtration). Estimating glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation.

Treatment with DRV/COBI

- Virological response: Plasma HIV-RNA viral load (copies/mL) 24 and 48 weeks after the switch.
- Immune response: flow cytometric counts of CD4+ T cells (cells/μL) 24 and 48 weeks after the switch.
- Lipid profile (cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), transaminases hepatic levels: aspartate aminotranserase (AST) and alanine transaminase (ALT) and renal profile (creatinine and glomerular filtration) 24 and 48 weeks after the switch. Estimating glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation.
- Adherence variable: The calculation was made with the following formula:

Percentage of adherence= number of units of total ART medication dispensed/number of units of planned ARV medication.

Planned units were considered necessary to comply with the treatment on the days included from the first dispensation to the last in the period of time considered for the calculation. The adhesion was calculated in 2 periods: 6 months before the change and after the change until the cut-off date of the study.

In the event that one of the patients had an admission to our hospital, the Pharmacy Service provided the ART during the entire hospitalization period. According to this, the adherence calculation also took into account the registration of dispensed medication by unit dose to hospitalized patients.

Statistical analysis of the data was descriptive. The values of the

variables were expressed as means ± standard deviation (SD), medians, ranges and percentages. It was considered that there were no ethical problems in the conduct of the study, since it was an observational study. The information collected was considered confidential and was used only in the professional field.

Results

Eighty two patients were included who started treatment with DRV/COBI monotherapy during the inclusion period. Patients with DRV/COBI represent a 5.25% of the total number of active patients with ART (N=1,562) in the same period of time in our hospital. Four patients were excluded, one because incomplete data and three patients because they did not met inclusion criteria. Hundred percent of the patients had a viral load <50 copies/mL during at least 6 months before the switch to DRV/r, and also met criteria according to GESIDA guidelines for switching to a monotherapy. Before switching to DRV/COBI, all patients had an undetectable viral load (<50 copies/mL).

Of the 78 patients evaluated, 73.08% were male and the mean age was 49.09 ± 9.58 years. Patients had a median of 31.29 (6-74.82) months with DRV/r monotherapy, previous to the switch to DRV/COBI monotherapy (taking into account that our computerized recordings began in 2008).

Hundred percent of the patients (N=78) had at least one different previous ART regimen to DRV/r monotheraphy; 55.13% (N=43) had two previous ART regimens and 14.10% (N=11) three previous ART regimens (Table 1).

The most commonly used ART regimen was 2 NRTIs+PI/r in all treatment lines, most specifically, triple therapy with tenofovir/disoproxil fumarate/emtricitabine (TDF+FTC) and a third antiretroviral (AR) drug (Table 2).

We can see the ART regimen immediately preceding the switch to DRV/r monotherapy (Figure 1).

The median time to treatment with DRV/COBI was 14.93 (9-20.61) months. The first and second control analysis after the switch to DRV/COBI was obtained at week 24 and 48.

The results at week 24 published recently by Yunquera-Romero et al. [15] showed that the 11.53% of the patients (9/78) had developed "blips" (Figure 2a). Four patients had presented one previous "blip" during treatment with another ART regimen prior to DRV/COBI monotherapy Three of these nine patients (33.34%) had a switch of treatment to ensure the effectiveness of ART (Table 3). At week 24 a 5.12% of the patients (4/78) had a viral load ≥ 200 copies/mL. A viral load of 200-1,000 copies/mL is associated with an increased risk of virological failure and selection of resistance mutations. These patients switched to another regimen ART too.

Previous ART regimen to DRV/r	1 previous ART	2 previous ART	3 previous ART
2NRTIs+PI/r	44	22	5
2NRTIs+NNRTI	19	6	1
NRTIs+1PI/r+INSTI	6	2	1
2NRTIs+INSTI	1	1	0
PI/r monotherapy	2	7	1
CCR5 antagonist +INSTI+ PI/r	2	0	0
INSTI + PI/r	2	2	1
2NRTIs+1PI/r +IINSTI	1	0	0
NRTIs+1PI/r	1	2	0
ICCR5+PI/r	0	0	1
NNRTI+INSTI	0	0	1
TOTAL PATIENTS	78	42	11

NRTIs: Nucleotide/Nucleoside Reverse-Transcriptase Inhibitors; PI/r: Ritonavir-Boosted Protease Inhibitor; NNRTI: Nonnucleoside Reverse-Transcriptase Inhibitor; INSTI: Integrase Strand Transfer Inhibitor; CCR5 Antagonist: C-C Chemokine Receptor Type 5 Antagonist.

Table1: Previous ART regimen to DRV/r monotherapy.

TDF+FTC+third AR drug	First-line ART	Second-line ART	Third-line ART
TDF+FTC+RPV	1		1
TDF+FTC+NVP	4		
TDF+FTC+LPV/r	11	4	
TDF+FTC+FPV/r	6		
TDF+FTC+EFV	9	1	
TDF+FTC+DRV/r	7	10	1
TDF+FTC+ATV/r	5		1
TDF+FTC+ETR		2	
TDF+FTC+FPV/r		2	
TOTAL PATIENTS	43	19	3

Table 2: Number of TDF+ FTC-based regimens plus a third antiretroviral (AR) drug previous to DRV/r monotherapy.

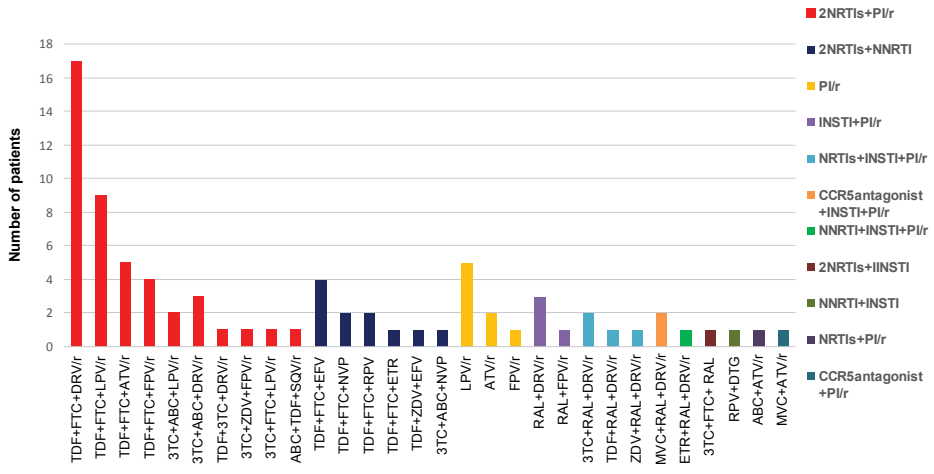

Figure 1: ART régimen immediately preceding the switch to DRV/r monotherapy.

The second control analysis was obtained at week 48. Three of the six patients who continued with DRV/COBI monotherapy despite the "blips", developed new "blips" at week 48. At week 24, after the switch to DRV/COBI, the median viral load of these three patients was 68.81 copies/mL (60-135.5). At week 48, the median viral load of these three patients was 101.5 copies/mL (80-119.5). However, their treatments were not changed. The other three patients who had "blips" at week 24 achieved a viral load <37 copies/mL at week 48 (Figure 2b).

Furthermore, from week 24 to 48, five more patients changed their treatment, two patients switched to DRV/r monotherapy again, one due to intolerance (vomiting and dizziness) and the other for unknown reasons, one patient switched to TAF/FTC/EVG/COBI coformulated due to side effects such as headache and two patients switched to DTG monotherapy, one of them due to interactions with ledipasvir/sofosbuvir and another related to the interaction with drugs prescribed by the general practitioner. In total, 66/78 patients continue currently with DRV/COBI.

Despite "blips", virological rebounds and switch in treatments, 95.45% (63/66) of the patients with DRV/COBI monotherapy were maintained with a viral load <37 copies/mL at week 48 of the follow-up.

Respect to the CD4+ T cells count (cells/μL), during the treatment with DRV/r the median was 691 (119-1,722) and 671 (4-1,492) with DRV/COBI at week 24 and 750 (188-1,705) at week 48.

We also analyzed the lipid profile hepatic and renal function of the patients before and after the switch at week 24 and at week 48. As for the lipid profile, there were no significant differences in cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels during treatment with DRV/r and after the switch to DRV/COBI (Figure 3).

In relation to the creatinine values of the patients, the median was 0.92 ± 0.64 mg/dL during the treatment with DRV/r and 1.05 ± 0.70 mg/dL and 1.07 ± 0.87 mg/dL during the treatment with DRV/COBI at week 24 and 48, respectively. Respect to renal function, mean GFR according to the CKD-EPI equation was 84.75 ± 13.57 ml/min (DRV/r monotherapy). At week 24 and 48 with DRV/COBI monotherapy was 79.65 ± 16.05 ml/min and 80.48 ± 16.16 ml/min respectively (Figure 4).

For the study of hepatic function, we analyzed the AST and ALT transaminase levels of patients during treatment with DRV/r and DRV/COBI. The following values were obtained: AST: 30.29 ± 5.22 U/L and ALT: 37.76 ± 34.44 U/L during treatment with DRV/r. After the switch

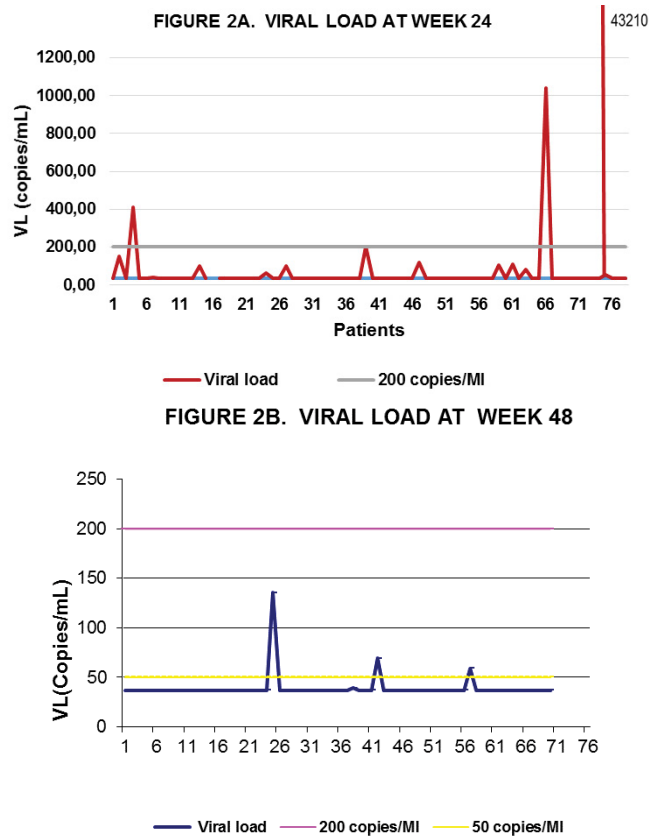

Figure 2: Viral load (copies/mL) at week 24 (A) and 48 (B).

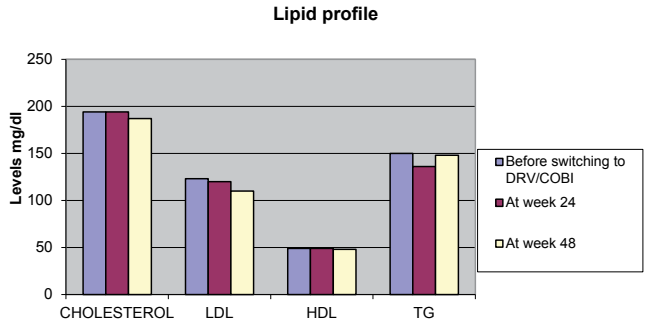

Figure 3: Lipid profile before and after switching to DRV/COBI.

PATIENT	Number of "blips" previous to DRV/COBI	VL during treatment with DRV/r (copies/mL)	CD4 during treatment with DRV/r (cells/μL)	VL during treatment with DRV/COBI (copies/mL)	CD4 during treatment with DRV/COBI (células/μL)	SWITCH
1	1	<37	1.204	151,3	1.469	
2	1	<37	1.001	101	1.381	
3	no	<37	469	65	454	
4	no	<37	644	101,5	817	
5	1	<37	386	119,7	4	TDF+FTC+DRV/COBI
6	no	<37	1.100	104	1.120	DTG+DRV/r
7	no	<37	1.145	110,6	963	
8	1	<37	894	80	534	
9	no	<37	691	53,34	562	ABC+3TC+DRV/COBI

Table 3: Patients who developed "blips" after switching to DRV/COBI. Viral load (copies/mL) and CD4+ T cells count (cells/μL), before and after switching.

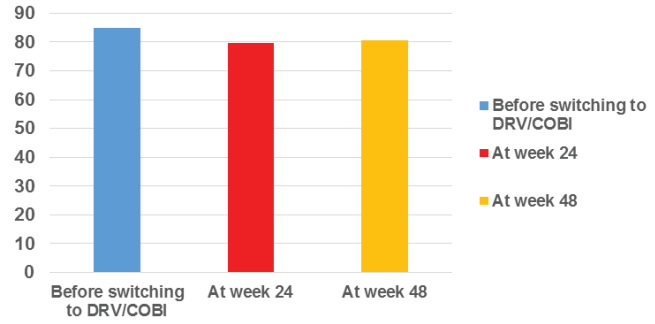

Figure 4: Estimation of Glomerular Filtration Rate (ml/min) before and after switching to DRV/COBI.

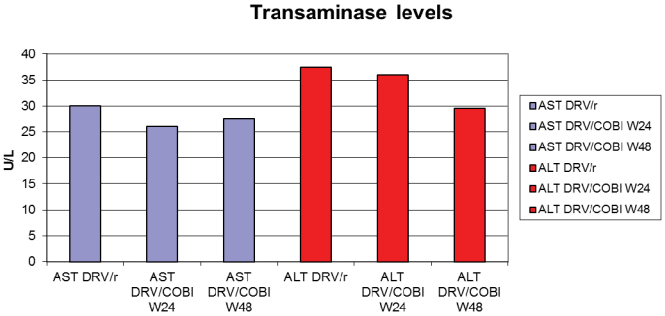

Figure 5: Transaminase levels before and after switching to DRV/COBI.

to DRV/COBI, the level at week 24 was 26.31 ± 11.47 U/L for AST and 35.97 ± 20.26 U/L for ALT. Finally, at week 48, the value for AST was 27.5 ± 16.62 and 29.5 ± 25.30 U/L for ALT (Figure 5).

The study did not reveal difference regarding adherence to treatment: 94% ± 7.96% for DRV/r monotherapy and 94% ± 7.40% and 95% ± 1% for DRV/COBI monotherapy at week 24 and 48 respectively.

Discussion

PI/r monotherapy does not represent the current gold standard of ART regimen, but it is included in some treatment guidelines such as the European AIDS Clinical Society (EACS) [3]. PI/r monotherapy with DRV/r or DRV/COBI qd or LPV/r bid might represent an option in people with intolerance to NRTIs or for treatment simplification or in recreational drug users with documented frequent interruption of combination antiretroviral treatment (cART). This strategy is associated with more virological rebounds than continuing triple therapy. However, resistance occurs rarely, and suppression can be regained with nucleoside reintroduction. In the recommendations of GESIDA guidelines 2016 [1], it is considered that there is not enough evidence to recommend a proactive switch to DRV/r or LPV/r monotherapy in patients who meet the criteria for the use of this strategy. Anyhow, the panel finds that there is also no evidence to oppose the use of monotherapy with DRV/r or LPV/r if the clinician wants to avoid or prevent adverse effects caused by NRTIs. Factors predicting the success of monotherapy are high adherence, prolonged and profound virological suppression, and nadir CD4>100 cells/μL. Monotherapy is placed in category B-I (DRV/r or LPV/r) [1]. Monotherapy with PI/r, however, is not recommended in other treatment guidelines [2,16,17].

Recently, a meta-analysis [18] has been published about the efficacy of PI/r as monotherapy. The aim of this analysis was to review the evidence and update a meta-analysis evaluating the efficacy and safety results from randomized controlled trials (RCTs) of ritonavir-boosted PI/r monotherapy. There were 2,303 patients from 13 different randomized clinical trials of DRV/r monotherapy (n=784: MONET [8], MONOI [9,19], Monarch [10] and PROTEA [11]), LPV/r monotherapy (n=829: OK pilot, OK-04, KalMo, KALESOLO, KRETA, MOST and DREAM), atazanavir/r monotherapy (n=103: MODAT), or all three (n=587: PIVOT). HIV-1 RNA plasma suppression was lower in the PI/r monotherapy arm compared with the triple therapy arm in the switch-equals-failure analysis, but not when intensification was included. Rates of resistance mutations were similar between arms, as was overall neurocognitive function. Even with the inclusion of the results from new studies, the findings of the present study are similar to those of two previous meta-analyses [20,21].

There were three key limitations to this analysis. First, all of the studies included were open-label, with no placebo- controlled trials. Therefore, there is a risk of ascertainment bias in these studies, if clinicians and patients were aware of the potential for CNS adverse events from PI monotherapy. Secondly, the "pure ITT" or "switch-included" endpoint may have been interpreted differently across the studies – long-term follow-up after switching off randomized medication is essential for this endpoint to be collected. Thirdly, PIVOT trial [22,23] could not be included in the main analyses of efficacy, because the data had been presented using Kaplan-Meier curves, which were not consistent with the analyses of the other trials at fixed time-points.

In summary, PI/r monotherapy appears to be a promising strategy for the maintenance of virologic efficacy, for patients who are fully suppressed, with higher CD4 nadirs and who are likely to remain adherent to treatment. The need for regular monitoring and the high rates of NRTIs reintroduction may offset some of the potential benefits of PI/r monotherapy; however, this needs to be further evaluated. PI/r monotherapy is unlikely to result in a significant difference in neurological impairment compared with triple therapy; however, viral load suppression in the CSF warrants further investigation.

Focusing on the clinical trials carried out with DRV/r, four studies were evaluated (N=784 patients): MONET, MONOI, Monarch and PROTEA. In all of them, DRV/r monotherapy vs 2 NRTIs+ DRV/r were studied. For the primary efficacy end point: undetectable viral load at week 48, a follow-up of 144, 96, 48 and 96 weeks respectively was performed in each of the studies.

PROTEA [11] is a randomized controlled trial to assess the efficacy and safety of DRV/r monotherapy as an alternative to triple therapy. In this study, in patients with HIV-1 RNA <50 copies/mL at baseline, switching to DRV/r monotherapy showed lower efficacy *vs.* triple therapy at week 96 in the primary ITT switch-equals-failure analysis, particularly in patients with CD4 counts <200 cells/μL.

These results are in consonance with the meta-analysis of Arribas et al. [18], where there were virological rebounds in the PI/r monotherapy arms, although this rebounds disappeared when reintroduction of the NRTIs was permitted.

DRV/r or LPV/r monotherapy has not demonstrated long-term non-inferiority versus triple therapy in ITT analyzes if the switch in randomized therapy is considered equal to failure. Non-inferiority has been demonstrated in the pure ITT or "switch included" analyzes (ignoring treatment switch, essentially the reintroduction with NRTIs). There is no agreement on which of these analyzes is most clinically relevant [1].

In June 2015 DRV/COBI co-formulated is commercialized in Spain. It is a combination of fixed doses of DRV and COBI that acts as a pharmacokinetic booster. Until the onset of COBI, DRV was used in combination with RTV, used as a booster, at low doses. When RTV is used at these doses, there is a potential risk that the HIV-1 virus develops resistance mechanisms by being a drug with antiretroviral activity [5]. In general, accumulated mutations associated with RTV resistance may decrease susceptibility to other PI due to cross-resistance. COBI, on the other hand, has no antiviral activity [12].

The effectiveness of DRV/COBI was based on the analysis data at week 48 obtained from the study GS-US-216-130 [12] and the ARTEMIS [6] and ODIN [7] clinical trials. In the GS-US-216-130 [12], of the 397 patients screened, 313 were enrolled and included in the intent-to-treat (ITT) population. The primary efficacy endpoint was the proportion of patients who achieved a HIV-1 RNA viral load <50 copies/mL at week 24 and 48, and the primary safety target was adverse events and clinical laboratory testing at week 24 of treatment. They explored the population pharmacokinetics of DVR and COBI and the analysis of the development of genotypic and phenotypic resistance in subjects experiencing virological failure. Virological response at week 24 and week 48 was achieved in 82% and 81% of subjects without pre-treatment respectively and in 50% of subjects with prior ART at week 48.

The ARTEMIS study is a randomized, controlled, and open-label study comparing the efficacy, safety and tolerability of DVR/r compared to LPV/r in naive patients with a plasma viral load ≥ 5,000 copies/mL. A fixed-dose TDF/FTC regimen was administered once daily in both groups.

The efficacy results obtained in trials GS-US-216-130 and ARTEMIS at week 48 were similar: 82.7% *vs.* 83.7%, respectively. Among pretreated patients with previous failure, this comparison is not adequate because of the small number of patients in the GS-US-216-130 trial (N=18).

The GS-US-216-130 study is the only pivotal trial used for the approval of a drug with an open clinical trial methodology of a single treatment arm. This methodology presents some limitations to perform an assessment and positioning with the drugs used for the same pathology. There are no clinical studies comparing DRV/COBI with DRV/r or any other treatment regimen.

In our study, all patients had previously been treated with DRV/r monotherapy, had viral load <37 copies/mL and had no PI-resistance mutations.

However, not all patients had undetectable viral load after switching to DRV/COBI: at week 24 nine patients had "blips" and four patients had a viral load ≥ 200 copies/mL. Twelve patients switched their ART regimens, so at week 48, only 66 of the 78 patients continued with DRV/COBI monotherapy. Three patients continued with “blips” at week 48. Isolated "blips" have no clinical repercussions. However, frequent "blips" have been associated with increased risk of virological failure and onset of MR. In the presence of "blips" it is recommended to evaluate the adherence and the genetic barrier of the ART. Of the patients with "blips" at week 24, 55.5% (5/9) observed that they had a treatment adherence <90%, but equal to that they had when treated with DRV/r and had viral load <37 copies/mL, so this fact would not explain this virological rebound. We do not have resistance studies of patients with virological failure, but we do know that when they were with DVR/r they did not present MR to IP/r. There is no consensus regarding the optimal treatment of patients with detectable viral load but with a viral load <200 copies/mL. If the genotypic study does not show MR, it is recommended to maintain the same ART. Although the regimen has to be of high genetic barrier, according to the current GESIDA treatment guidelines [1].

Despite "blips", virological rebounds and switch in treatments, 95.45% (63/66) of the patients with DRV/COBI monotherapy were maintained with a viral load <37 copies /mL at week 48 of follow-up, which made it possible to simplify their antiretroviral treatment to a single daily tablet with the convenience that this represents for the patient without losing effectiveness. These results are in line with those obtained in other studies where monotherapy with PI/r has been studied.In addition there has been a slight increase in the CD4+ T cells count (cells/μL) from week 24 to 48.

COBI has as a special peculiarity to inhibit renal transporters of MATE tubular organic cations 1 and in this case, as well as RTV, organic anions, which results in a reduction of tubular secretion of creatinine and therefore in an increase in about 15% of plasma creatinine values.

This, however, does not have to translate into an alteration of the FG [23]. In our study, however, a slight decrease in mil/min of GFR during treatment with DRV/COBI was observed, at week 24 and 48. In the rest of the safety parameters (lipid and hepatic profile) DRV/COBI is similar to DRV/r.

The virological failure could be related to the pharmacokinetic characteristics of the potentiating drugs cobicistat and ritonavir. DRV/COBI pharmacokinetic studies have shown that there is clear and repeated bioequivalence demonstrated in Cmax and AUC between DRV/COBI and DRV/r, but the Cmin/C0h parameter has failed to demonstrate bioequivalence according to criteria predefined by the researchers in the studies between DRV/COBI and DRV/r [24].

Lambert-Niclot et al. [25] attempt to explain the factors associated with failure to monotherapy with DRV/r. They conclude by saying that the risk of virological failure is greater with monotherapy with DRV/r than with triple therapy, so patients have to be carefully selected. The best candidates for DRV/r monotherapy would be patients with excellent adherence and HIV RNA levels <50 copies/mL. The risk of virological failure would be lower among patients with long ART regimens who achieved virologic suppression before switching to a monotherapy regimen. Long-term ARTs in patients could result in lower residual viremia levels and lower pro-viral HIV-DNA levels.

A retrospective study by López-Cortés et al. [26] concluded that switching to PI/r monotherapy achieves sustained virological control in most patients, even in those with previous virological failures on PI-based regimens as long as no major resistance mutations are present for the administered drug.

Recently the new recommendations of the GESIDA guidelines (2017) have been published. In them, they appear new definitions of “blips” and virological failure that could modify the interpretation of the results of our study. Monotherapy is now placed in category C-I (DRV/r or LPV/r). There is no data on the efficacy of cobicistat-boosted DRV monotherapy, so this regimen cannot be recommended at the present time. Since DRV/r or LPV/r monotherapy has a greater risk of virological rebound than dual therapy with DRV/r or LPV/r +3TC, the committee recommends the use of monotherapy only in infrequent cases where dual therapy cannot be used [27].

Despite this, in view of our results at week 48, DRV/COBI monotherapy appears to be effective and safe (lipid, hepatic and renal profile). The main limitations of our study are, on the one hand, the small sample size to be able to draw reliable conclusions as to which monotherapy regimen is the most effective and on the other hand, that it is an observational study, and specific studies should be designed who compared DRV/r vs. DRV/COBI monotherapy to confirm these results.

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