Efficacy and tolerability of switching to a dual therapy with darunavir/ritonavir plus raltegravir in HIV-infected patients with HIV-1 RNA ≤50 cp/mL

Giordano Madeddu [1], Stefano Rusconi [2], Alessandro Cozzi-Lepri [3], Simona Di Giambenedetto [4], Stefano Bonora [5], Alessia Carbone [6], Andrea De Luca [7], Nicola Gianotti [6], Antonio Di Biagio [8], Andrea Antinori [9] for the Icona Foundation Study Group

[1]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Sassari, Italy [2]Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Italy;[3]Department of Infection & Population Health Division of Population Health, Hampstead Campus, University College London, London, United Kingdom; [4]Catholic University of the Sacred Heart, Milan, Unit of Infectious Diseases, Agostino Gemelli Polyclinic Foundation, Rome, Italy; [5]Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Italy;[6]Infectious Diseases Department, San Raffaele Scientific Institute, Università vita e salute, Milan, Italy; [7]Division of Infectious Diseases, Department of Medical Biotechnologies, University of Siena and Siena University Hospital, Siena, Italy; [8]Unit of Infectious Diseases, IRCCS San Martino Hospital - IST, Genoa, Italy; [9]Clinical Department, National Institute of Infectious Diseases 'Lazzaro Spallanzani', Rome, Italy;

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Corresponding author
Giordano Madeddu, MD
Unit of Infectious Diseases,
Department of Clinical and Experimental Medicine, University of Sassari
Viale San Pietro 8
07100 Sassari
Tel +39 079 228776 (4330) Fax +39 079 228781
e-mail: giordano@uniss.it

ABSTRACT

BACKGROUND

Nucleos(t)ide reverse transcriptase inhibitors (NRTI) toxicity may represent a threat for long term success of combined antiretroviral therapy. Some studies have suggested a possible improvement of NRTI related toxicity after switching to NRTI-sparing regimens.

OBJECTIVES

We aimed to explore the efficacy and tolerability of switching to darunavir/ritonavir (DRV/r) plus raltegravir (RAL) while having a viral load (VL) ≤50 copies/mL in the clinical setting.

STUDY DESIGN

Treatment-experienced HIV 1-infected patients enrolled in the ICONA Foundation Study cohort were included if they switched from a three-drug regimen to DRV/r+RAL with a HIV-RNA≤50 copies/mL. Different definitions of virological failure (VF) and treatment failure (TF) were employed. Kaplan-Meier curves and Cox regression models were performed to estimate time to event probability.

RESULTS

Seventy-two patients were included, 22 (31%) female, 31 (43%) men who have sex with men (MSM), 15 (21%) had hepatitis co-infections. Median age was 44 (IQR: 35-50) years, CD4 cell count was 389/mmc (283-606). Median follow up time for TF was 24 (IQR 9-31) months. Twenty-five discontinuations occurred (60% simplifications), only 2 (8%) were toxicity-driven (lipid elevations). The probability of VF (confirmed VL>50 copies/mL) was estimated as 7% [95% confidence interval (CI) 1-13%] by 12 and 9% (95% CI 2-16%) by 24 months. When considering TF, we found a probability of stop/intensification/single VL>200 copies/mL of 13% (95% CI:1-17%) and 22% (95% CI:11-33%) by 12 and 24 months. Female gender (adjusted relative hazard, ARH=0.10; 95% CI:0.01-0.74; p=0.024) and older age (AHR=0.50 per 10 years older; 95% CI:0.25-0.99; p=0.045) were associated with a lower risk of TF. A previous PI failure was strongly associated with TF (AHR=52.6, 95% CI:3.6-779; p=0.004).

CONCLUSIONS

DRV/r+RAL is a valuable NRTI-sparing option, especially in female and older patients, with a relatively low risk of VF and good tolerability after 2 years since start in an ART-experienced population. However, previous PI-failure should be a limiting factor for this strategy.

BACKGROUND

Nucleos(t)ide reverse transcriptase inhibitors (NRTI) toxicity may represent a threat for long term success of combined antiretroviral therapy (cART) [1-3]. Some studies have suggested a possible improvement of NRTI related toxicity after switching to NRTI-sparing or single NRTI-including regimens [4-6]. In a recent study conducted in patients receiving a successful multidrug salvage regimen with at least two active drugs including a boosted protease inhibitor (PI), the withdrawal of NRTI was safe [7]. Two NRTI plus a third drug a PI, an integrase inhibitor (INI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) still represent the cornerstone for cART initiation in naïve patients, and the International and National treatment Guidelines do not recommended NRTI-sparing regimens in the first-line [8-11].

Although most studies were conducted in the scenario of antiretroviral-naïve patients, in clinical practice, this NRTI-sparing regimen is been employed in different strategies (salvage, simplification, switching). Other studies suggest that the combination is indeed widely used, at least in Spain and Italy [7, 12-14]. A recent study by Calza et al. showed that in 82 virologically suppressed patients without history of PI failure the combination of RAL+DRV/r was capable of maintaining a virologic success in more than 92.7% of cases at 48 weeks with a significant improvement of lipid profile and reduction of tubular proteinuria [15].

OBJECTIVES

In this analysis, we aimed to investigate the risk of virological failure (VF), and tolerability of switching to DRV/r plus RAL while having a viral load (VL) ≤50 copies/mL in an unselected population from the real life setting.

STUDY DESIGN

Treatment experienced HIV-1-infected patients enrolled in the ICONA (Italian Cohort Naïve Antiretrovirals) Foundation Study cohort were included in this analysis if they underwent a switch to a DRV/r+RAL with an HIV-RNA ≤50 copies/mL (baseline). No patient had previous exposure to integrase inhibitors. Virological failure (VF) was defined as a confirmed HIV-RNA>50 copies/mL (two consecutive values). We also investigated the risk of treatment failure (TF) defined as single HIV-RNA>200 copies/mL, intensification or discontinuation of DRV/r+RAL for any reason. Glomerular filtration rate was estimated using the CKD-EPI formula [16]. A range of methods were used to measure HIV-RNA according to availability at the participating sites. The most frequent were Real time Abbot PCR (n=10, 13%), NASBA (n=4, 6%) and Roche (n=3, 4%).

We performed time to event estimates using Kaplan-Meier curves and Cox regression models. Covariates in the final model included the number of failures on regimens containing a PI, gender, mode of HIV transmission, HBV/HCV co-infection, calendar year of switch, age, CD4 nadir count, CD4 count at cART initiation, viral load at cART initiation and duration of viral suppression <50 copies/mL.

RESULTS

Seventy-two patients were included, 22 (31%) female, 31 (43%) MSM, 15 (21%) had hepatitis co-infections (10 with HCV and 5 with HBV). Median baseline characteristics were: age 44 [Interquartile range (IQR): 35-50] years, CD4 cell count was 389/mmc (IQR: 283-606); HIV-RNA at initiation of cART was 4.22 (IQR: 2.92, 6.54) $\log_{10}$ copies/mL and total median duration of HIV-RNA ≤50 copies/mL 5 months (IQR: 1-53). Time from initiation of previous ART was 3 (IQR: 1-30) months and median time from first starting antiretrovirals to the switch to DRV/r+RAL was 10 months (IQR: 1-109). Seventyfour (88.9%) patients were receiving a boosted PI at baseline and 14 (19%) patients previously failed virologically a PI-based cART before baseline. On average

participants have been previously exposed to 2 lines of treatment (IQR:1-5), for 65% the dual regimen was the 4th therapy started. Forty-eight of the 72 patients (67%) were already receiving darunavir/r prior to switching to the dual regimen.

Median total cholesterol levels were 180 (IQR: 155-224) mg/dl, HDL 45 (IQR: 35-54) mg/dl and triglycerides 106 (IQR: 75-156) mg/dl. Complete baseline patients characteristics are shown in Table 1. The median follow up time for the composite endpoint was 24 (IQR 9-31) months. The median follow-up time by gender was 24.5 months (IQR: 12-31) in males and 17.5 (5-33) in females. The proportion of people with at least 24 months of follow up was 27/50 (54%) among males and 10/22 (45%) among females.

Overall, we observed 30 discontinuation events of the dual regimen. However, regimen simplification in terms of pill burden was the most frequent cause of discontinuation and occurred in 15 out of 30 patients (50%), 14 of whom discontinued RAL, whereas toxicity driven interruption occurred only in 3 (10%) cases (1 lipid elevation, 1 renal and 1 central nervous system toxicity). The remaining causes of discontinuations included patients' decision in 2 (7%) and drug-drug interactions, compliance with guidelines, virological failure, immunological failure, regimen intensification, death, temporary stop (physician's decision) in 1 (3%) case each. In 2 (7%) patients the cause of discontinuation was unknown.

Table 2 shows the number of patients experiencing VF and TF and the Kaplan-Meier estimates by 12 and 24 months respectively, for each of the adopted endpoints. The probability of VF defined as confirmed VL>50 copies/mL was 7% [95% confidence interval (CI):1-13%] by 12 months and 9% (95% CI 2-16%) by 24 months. When considering the composite endpoint of TF we found a probability of stop/intensification and single value of VL>200 copies/mL of 13% (95% CI:1-17%) and 22% (95% CI:11-33%) by 12 and 24 months, respectively.

Still considering the composite TF endpoint defined as stop/intensification and single value of VL>200 copies/mL, from fitting a multivariable Cox regression analysis, female gender (adjusted relative hazard, ARH=0.10; 95% CI:0.01, 0.74, p=0.024) and older age (AHR=0.50 per 10 years older; 95% CI:0.25-0.99, p=0.045) were associated with a lower risk of TF. Having previously experienced virological failure to a PI-based regimen was the strongest predictor of failure of the dual strategy (AHR=52.6, 95% CI:3.6-779, p=0.004). In contrast, viral load at starting cART, CD4 cell nadir and hepatitis coinfections were not associated with increased risk of TF (Table 3).

Historical genotypes were available for 47/72 (65%) patients. When looking at the virological endpoint of time to a single VL>200 copies (part of the composite outcome) those with major IAS PI resistance mutations (2/5, 40%) showed a higher risk of failure compared to those without (8/34, 19%) but the difference was not statistically significant (chi-square p=0.28). The univariate Hazard ratio (HR) for failure from fitting a univariable Cox regression model was 2.12 (95% CI: 0.80-5.66, p=0.13) for those with PI resistance vs. no PI resistance detected.

When looking at the endpoint of confirmed VL>50 copies/ml results were similar with patients with major PI resistance mutations (2/5, 40%) showing an increased risk of failure compared to those without (6/42, 14%, p=0.15). The univariable HR for virological failure was 2.95 (95% CI: 1.03- 8.27, p=0.04).

Mean (SD) CD4 count were 471 (164) cells/mm^3 by 3 months, 518 (213) 6 months, 552 (194) 9 months, 533 (203) by 12 months and 599 (108) by 24 months.

As far as tolerability and lipid, renal and liver disease indicators profiles, we did not find any significant modification of total cholesterol, high density lipoproteins (HDL), triglycerides, eGFR and alanine transaminase (AST) levels over 24 months (Figure 1).

DISCUSSION

Current guidelines suggest the use of a combination of three antiretroviral drugs as initial therapy, including 2 NRTIs plus 1 PI/r, 1 integrase inhibitor or 1 NNRTI [8-11]. However, taking into account the rising evidence of nucleoside analogues long-term toxicity, NRTI-sparing strategies are being used in clinical practice.

We showed that, in an unselected patient population, representative of the clinical practice setting in Italy, a dual therapy including DRV/r+RAL seems to be moderately effective and tolerated over an average follow-up of two years. We found a relatively low probability of VF (considering both confirmed VL>50 or single value of VL>200 copies/mL) ranging between 9 and 15% by 24 months from the time of switch. When we compared our results with those of the study by Calza et al. in a similar patient population we found higher rates of pure virological failure at 48 weeks (7% vs 2.4%). However, it should be considered that in the study by Calza et al patients with previous failure to PI containing regimens were excluded thus probably explaining the observed difference [15].

When considering the composite outcome of TF we observed a probability of 13% and 22% of failure at 12 and 24 months for the conservative definition of a single value of VL>200 copies/mL and stop/intensification. This result is in line with previous observational data on triple therapy in the observational cohort studies [17, 18].

Female gender and older age were independently associated with significantly lower risk of TF. It is possible that, at least older age could represent a marker of better adherence [19, 20]. In general, these results are reassuring since older patients and females are also typically more likely to develop drug toxicity and therefore also those who seem to benefit the most from this dual therapy strategy which showed only a few adverse event-driven discontinuations [21].

Contrary to what found in PI/r monotherapy studies [22, 23], we did not find an increased risk of TF in patients with shorter duration of viral suppression, low nadir CD4 and with hepatic co-

infections, suggesting that DRV/r+RAL might be used safely by a larger proportion of individuals. Having previously failed a PI-based regimen was strongly associated with TF. Furthermore, we showed that the presence of major IAS PI resistance was associated with an increased HR of virological failure, especially when considering a confirmed VL>50 copies/mL. Therefore, a previous failure of a PI-based regimen, especially if major IAS PI resistance mutations are detected, should remain a main limiting factor when selecting people for this strategy.

Our results also suggest that RAL+DRV/r is generally safe with a probability of discontinuation due to adverse events of 10% by 2 years.

We showed no significant modification in lipid profile whereas Calza et al evidenced a significant reduction in triglyceride levels after 48 weeks [15]. However, in that study, baseline mean triglyceride values were above the normal range (286 mg/dL) compared to our patients that showed a median of 106 (IQR: 75-156) mg/dl. Since our patients started from normal levels no further benefit was expected and our data suggest that the combination of DRV+ RAL was not associated with a worsening in lipid profile.

Our results also showed a non-significant modification of eGFR during 24 months of follow up as also suggested by Calza et al and highlight the renal tolerability of the combination [15].

Our data also showed a trend to increase in CD4 cell count over time which is in line with the significant increase shown by Calza et al at 48 weeks [15]. However, since only a few patients had available data at each follow up time, we think it is fair to say that bigger studies are needed to confirm this result.

Most regimen discontinuations were due to treatment simplification (15, 50%) and twice daily RAL was the drug stopped probably due to the fear of selected non-adherence to one of the two daily doses. However, only a minority of discontinuations was due to virological failure (1, 3%) and toxicity (3, 10%) over 2 years. Adherence is a complex phenomenon that implies acceptance of

the diagnosis and motivation to carry out the treatment, possession of appropriate skills, ability to overcome any difficulties that appear to maintain the level of treatment success over time. In patients with multiple previous cART regimen tolerability may favor adherence more than the daily schedule. Although once daily dose is the goal to improve adherence, it is not always superior to twice daily dosing in terms of virologic success. In a systematic review of 19 clinical trials Nachega et al evidenced that once daily therapy is associated with better adherence but non with better virologic results [24]. Another recent study by Arroyo et al found no difference in adherence rates in patients receiving once or twice daily regimens [25]. A French study showed that non-adherence was independently associated with side effects, and having a three times or more daily dosing regimen in comparison to once or twice daily therapy [26].

The upcoming availability of 1200 mg once daily RAL and the present possibility to use co-formulated DRV/Cobicistat could represent a future advantage of the combination of DRV+RAL in virologically suppressed patients.

The main limitation of our analysis is the lack of a control group to compare the failure estimates of the dual DRV/r + RAL regimen to that of a standard triple cART. In particular, it is not obvious to set a threshold below which the proportion of failure of this strategy is too high to be acceptable (compared to remaining on triple regimens for example). In this case even the historical controls are not fully comparable as performed in the context of first-line cART. Furthermore, since only a minority of patients were switched from triple cART to DRV/r + RAL, this study is not useful to evaluate the potential advantages after switching from a triple to a dual NRTI-sparing regimen.

In conclusion, switching to DRV/r + RAL in clinical practice is a valuable NRTI-sparing regimen, with a relative low risk of VF (7-9%) and good tolerability after 2 years since start in an antiretroviral-experienced population. Of note, female and older patients, both vulnerable populations, seem to have greater benefits from this strategy. Larger studies are needed to establish more solid criteria

for selecting people who might benefit from this dual regimen but previous failure of a PI-based ART should represent a limiting factor for this strategy.

Ethics approval and consent to participate

All patients enrolled gave written, informed consent to participation in the ICONA Foundation cohort study and the study was approved by each of the Ethics Committees from the sites participating to the ICONA Foundation Study.

Conflict of interests

GM has been advisor for Gilead Sciences, Janssen and Merck Sharp and Dohme and ViiV Healthcare and has received speakers' honoraria from Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, Janssen and ViiV Healthcare; SR has received research grants from Gilead Sciences, Janssen, ViiV Healthcare and consultancy honoraria and speaking fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Janssen and ViiV Healthcare; ACL declares non conflict of interest; SDG received speaker's honoraria from Bristol Myers Squibb, Janssen, Merck Sharp & Dohme and ViiV Healthcare; SB has received speaker's honoraria, travel grants or advisory board honoraria from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV Healthcare, AC declares no conflict of interest; ADL received research grants from Gilead Sciences, Merck Sharp and Dohme, ViiV Healthcare and consultant fees from AbbVie, Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme, ViiV Healthcare and Janssen; NG has been advisor for Abbvie, Gilead Sciences, and Janssen and has received speakers' honoraria from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, Roche, ViiV Healthcare and Janssen; ADB has been advisor for

AbbVie, Gilead Sciences and Merck Sharp and Dohme and has received speakers' honoraria from Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, Janssen and ViiV Healthcare; AA has received speaker's fees or travel grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV Healthcare and research grants from Bristol-Myers Squibb.

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Authors' contributions

GM, SR, ACL, ADB and AA contributed to study conception and design, analysis and interpretation of the data and drafting of the article; SDG, SB, ADL, AC and NG contributed to the analysis and interpretation of data and to the critical revision of the manuscript for important intellectual content; all authors gave final approval of the final manuscript.

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