Title

The effect of switching to Maraviroc + Darunavir/ritonavir dual therapy in virologically suppressed patients on the progression of liver fibrosis: findings from a randomized study

Running Title: Effect of MVC + DRV/r on liver fibrosis

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In vitro and animal studies revealed a potential protective role of CCR5-antagonists on reducing liver fibrosis progression and protecting from developing hepatocellular carcinoma. [1] Hepatocytes bear CXCR4 and CCR5, the two main co-receptors for HIV entry into cells, and the blockade of co-receptors on hepatic stellate cells, the major producers of extracellular matrix in the liver, will slow progression of liver fibrosis, especially due to HIV-envelope gp120-mediated fibrogenesis modulation. [2-5].

The aim of present analysis was to compare the evolution of liver fibrosis over time evaluated by surrogated biomarker assays in HIV-1 infected patients on a virologically successful antiretroviral therapy (stable HIV-1 RNA <50 copies/mL), randomized to switch to maraviroc + darunavir/r (MVC + DRV/r arm) qd or to continue the current maraviroc-free 3-drug ART (3-drug ART arm).

Patients included in the study were enrolled in the GUSTA (GUided Simplification with Tropism Assay) trial, a multicenter, open-label, randomized study (www.clinicaltrials.gov, number NCT01367210), whose main results have been published [6].
Briefly, GUSTA included patients with HIV-1 RNA <50 copies/mL for at least 6 months, R5 tropism and CD4 counts >200 cells/µL for at least 3 months before enrollment; HBV coinfected patients and those with Child-Pugh B/C cirrhosis were excluded.

We retrospectively evaluated Fibrosis-4 (FIB-4) Index and AST to Platelet Ratio Index (APRI) scores, at baseline and after 12, 24, 48 and 96 weeks. The cut-off points of serum marker tests of hepatic fibrosis were: FIB-4 <1.45 (F0-F1), 1.45-3.25 (indeterminate), >3.25 (F3-F4) and APRI <0.5 (F0-F1), >1.5 (F2) and >2 (cirrhosis).

Differences between arms were assessed by χ²-square and Student's t-test; longitudinal within group differences by McNemar test. The FIB-4 Index and APRI scores were employed as continuous variables; their predictors at baseline and their change over time were investigated by linear regression.

We included 150 patients, 76 randomized to MVC + DRV/r arm and 74 to 3-drug ART arm. Baseline characteristics were homogeneous between arms except for relative younger age in the MVC + DRV/r arm (median 47 yrs; IQR 40-52) than in the 3-drug ART arm (50 yrs; IQR 44-57) (p=0.08), more frequent African ethnicity in the 3-drug ART arm than in the MVC + DRV/r arm (8% vs. 1%) (p=0.05) and FIB-4 median value higher in the MVC + DRV/r arm (1.15; IQR 0.82-1.32) than in the 3-drug ART arm (0.91; IQR 0.68-1.20) (p=0.01). APRI score was similar between arms: 0.23 (0.18-0.29) in the MVC + DRV/r arm and 0.25 (0.20-0.33) in the 3-drug ART arm (p=0.12).

Overall, 89% (134/150) were males and Caucasians, 41% (61/150) were heterosexuals, (57/150) 38% homosexuals/bisexuals, 7% (10/150) reported history of injected drug use, 11 years of HIV (7-18), 10 years of ART (6-15), CD4 at nadir 222 cells/mm (132-319) and at baseline 654 cells/mm (506-905). Eighteen patients presented positive serology for HCV and 8 had a detectable HCV RNA, 4 in each arms.
Sixteen (11%) presented diabetes mellitus: 12% (9/76) in the MVC + DRV/r arm and 9% (7/74) in the 3-drug ART arm (p=0.04). At screening NRTIs were used in 95% (143/150), NNRTIs in 12% (18/150), INSTIs in 18% (17/150), PIs in 69% (103/150) of which boosted PI in 63% (94/150) and DRV/r in 31% (47/150). No differences between arms were observed in terms of dislipidemia (in 100/150, 66%), with total cholesterol 203 mg/dL (IQR 173-230), body mass index (23 kg/m^2, IQR 22-26) and glucose 89 mg/dL (IQR 82-100). Median value of false positive rate (FPR) at geno2pheno was 43 (IQR 24-69) with no differences between groups.

During observation in the 3-drug ART arm (n=74) NRTIs were used in 92%, NNRTIs in 16%, INSTIs in 15%, PIs in 69%, boosted PI in 51% and DRV/r in 43%.

According to the cut-off points of hepatic fibrosis FIB-4 in the MVC + DRV/r arm was <1.45 in 83% (63/76), between 1.45 and 3.25 in 16% (12/76) and >3.25 in 1% (1/76); in the 3-drug ART arm it was <1.45 in 88% (65/74), between 1.45 and 3.25 in 12% (9/74) (no one had FIB-4 >3.25).

Overall, APRI was <0.5 in 91% (137/150) and no one had >1.5 at baseline.

Based on the FIB-4 score, at 48 weeks progression to a higher level was observed in 6% (4/63) in the MVC + DRV/r arm and in 6% (4/65) in 3-drug ART arm; in 3% (4/12) among those in MVC + DRV/r arm and in 3% (3/9) in 3-drug ART arm FIB-4 improved at least one stage, while the other patients did not modify their FIB-4 stratum.

Based on the APRI score, at 48 weeks significant modification of stratum was no observed.

In addition, no significant differences between arms were observed in platelet counts and alanine transaminase changes at 48 weeks from baseline. We observed a more profound decrease of aspartate transaminase levels in the MVC + DRV/r arm (mean change -4.19 IU/L, SD 7.2) vs 3-drug ART arm (mean change +0.58 IU/L, SD 9.9) (p=0.007).
In a multivariable model adjusting for risk factor for HIV acquisition and duration of ART exposure, longer time from HIV diagnosis (per 1 year increase +0.031, 95% CI +0.007; +0.055, p=0.01), lower nadir CD4\(^+\) cells count (+100 cells increase, -0.060, 95% CI -0.107; -0.014, p=0.01) and HCV antibody positive status (+0.321, 95% CI +0.000; +0.642, p=0.05) were associated with higher baseline FIB-4 values. No factor independently associated with baseline APRI values was observed. During follow-up, the APRI score decreased more prominently in the MVC + DRV/r arm vs. 3-drug ART arm at week 12 (median change -0.77; IQR -1.11; -0.58 vs. -0.67; IQR -0.97; -0.46; p=0.02), at week 48 (-0.04; IQR -0.09; +0.02 vs. +0.001; IQR -0.037; +0.049; p=0.01) and at week 96 (-0.03; IQR -0.06; +0.01 vs. +0.02; IQR -0.01; +0.10; p=0.053).

In a multivariable model, predictors of APRI change at 48 weeks were baseline APRI (-0.391; 95% CI -0.515; -0.266; p<0.001) and MVC + DRV/r arm vs 3-drug ART arm (-0.040; 95% CI -0.006; -0.074; p=0.021).

FIB-4 also showed a trend towards a more prominent reduction in the MVC + DRV/r arm (-0.02; IQR -0.21; +0.13) vs. 3-drug ART arm (+0.02; IQR -0.23; +0.20) (p=0.35) at week 48. Baseline FIB-4 but not study arm predicted FIB-4 modifications during follow up.

In conclusion we observed that switch to MVC + DRV/r in HIV-1 infected, but virologically suppressed patients on 3-drug ART, was associated with a slight but significant improvement of the APRI score over time as compared to continuing 3-drug ART without maraviroc. This maraviroc-containing regimen did not significantly influence the longitudinal change of the FIB-4 score, possibly due to the presence of age as a component of the score, which was increasing over time in the study patients, although a trend towards an improvement was observed. Our observations are in agreement with experiments showing a reduction of hepatic stellate cells activation and fibrosis progression and an improved survival in a murine model of hepatocellular
carcinoma [1] and in vitro observations on the inhibitory effect of maraviroc on the accumulation of fibrillar collagens and extracellular matrix proteins by human hepatic stellate cells [7]. Results from this study are also in line with a previous retrospective non-comparative analysis on 71 HIV/HCV co-infected patients treated with maraviroc, showing a potential beneficial effect on liver fibrosis measured by the APRI score [8]. In a previous prospective, non-controlled pilot study on 24 HIV/HCV co-infected patients starting a maraviroc-based regimen, liver fibrosis was slightly but not significantly reduced, although observation was limited to 6 months [9]. In addition, a recent study suggests that a validated marker of liver fibrosis was reduced in HIV-1 infected patients carrying the variant allele CCR5 delta-32, associated with reduced CCR5 expression, and in patients exposed to cenicriviroc, a CCR5/CCR2 blockade agent [10].

Our study adds to previous evidence and has its strengths in the randomized comparison, the study arm treated with an homogeneous maraviroc-containing regimen and the prospective follow up of the patients up to 96 weeks. Its main limitation is the lack of information on the liver histological pattern modification rather than indirect biomarkers, as it remains unclear whether their change truly reflects hepatic fibrosis change. The lack of information on patients alcohol consumption and the absence of transient liver elastography measurements also represent limitations to this analysis. Further studies are warranted to confirm an anti-fibrotic effect of CCR5 antagonist therapy.

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References


Legend

Fig. 1 a APRI score during follow up
Fig. 1 b FIB-4 during follow up

No significant difference between arms at each time-point
Fig. 1a APRI score during follow up
Fig. 1 b FIB-4 during follow up

No significant difference between arms at each time-point