Sofosbuvir/Daclatasvir in HIV/HCV Co-infected Patients With Extensive Liver Fibrosis

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Abstract 650

Updated abstract

Background: All-oral combination of sofosbuvir (SOF), a pan genotypic HCV NS5B inhibitor, plus daclatasvir (DCV), NS5A inhibitor, has been poorly evaluated in HIV/HCV co-infected patients. Thus, interactions between this anti-HCV regimen and antiretroviral drugs (ART) have also been poorly investigated. We evaluated the safety and efficacy of SOF plus DCV and plasmatic concentrations of antiviral drugs in HCV/HIV co-infected patients.

Methods: HCV patients with extensive liver fibrosis (METAVIR F3 and F4) and stable HIV disease received SOF 400 mg QD and DCV (30, 60 or 90 mg QD) for 24 weeks. Trough plasma concentrations (C_{trough}) of DCV, sofosbuvir's major circulating metabolite (GS-331007) and ongoing ART were determined on patients' blood samples 15 days after starting HCV treatment. The primary efficacy endpoint was sustained virologic response 12 weeks after treatment discontinuation (SVR12).

Results: Baseline characteristics of the 26 patients are shown in Table 1 and Figure 1. HCV viral load under treatment was undetectable in 5/26 (19%) at Week 2 (W2), 12/25 (48%) at W4, 22/26 (85%) at W8, 24/25 (96%) at W12, 23/24 (96%) at W16, 21/21 (100%) at W20, and 20/20 (100%) at W24. SVR results are presented in Figure 2. During treatment, four patients experienced grade 3 or 4 adverse events. Pharmacological testing results are presented in Figures 3 and 4.

Conclusions: Interferon-free treatments for HCV are needed for HIV/HCV co-infected patients. Pharmacological testing of DCV and SOF is needed to assess possible drug-drug interactions (DDIs) with HIV antiviral therapy. Our preliminary data suggests that DCV plus SOF treatment is well-tolerated, safely co-administered with multiple ART regimens to patients with extensive liver fibrosis, with an efficacy similar to that observed in HCV mono-infection.

Introduction

All-oral combination of sofosbuvir (SOF), a pan genotypic HCV NS5B inhibitor, plus daclatasvir (DCV), an HCV NS5A inhibitor, is recommended in national [1] and international guidelines [2].

However, this association has been poorly evaluated in HIV/HCV co-infected patients [3]. Interactions between this anti-HCV regimen and antiretroviral drugs (ART) have been poorly investigated. We evaluated the safety and efficacy of SOF plus DCV and plasmatic concentrations of antiviral drugs in HCV/HIV co-infected patients.

Methods

Patients followed in the Nice University Hospital Internal Medicine and Infectious Diseases departments who initiated a 24 week treatment regimen between 04/16/2014 and 09/26/2014 and with the following inclusion criteria entered the study:

•HIV disease on stable ART not modified for 1 month,

•Extensive liver fibrosis METAVIR F3 and F4 in Fibroscan®. Validity criteria for liver stiffness evaluation were (1) ≥10 successful liver stiffness measurements; (2) IQR/median ratio <0.30 and (3) ≥60% measurement success rate. Cut-off points were as follows: F3 >9.5 – 14.5 kPA; F4≥14.5 kPA. Cirrhotic patients with Child-Pugh C score were not included.

Patients received SOF 400 mg QD and DCV QD for 24 weeks. Daily dosing of DCV was 30, 60 or 90 mg according to concomitant ART. HCV-RNA was measured at baseline and at 2, 4, 8, 12, 16, 20 and 24 weeks (W) following treatment initiation and sustained virologic response (SVR) was assessed at W4, W8 and W12 following treatment discontinuation. Grade 3 and 4 adverse events were collected.

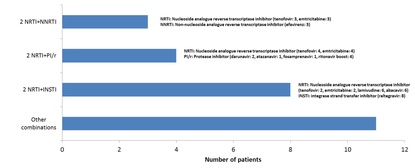
Trough plasma concentrations of DCV, SOF's metabolite (GS-331007) and ongoing ART were determined on patients' blood samples 15 days after starting HCV treatment. Due to the very short (0.4 hour) median elimination half-life of SOF, this prodrug was never detected in the available samples and thus, we decided to evaluate the pharmacokinetic behaviour of the main circulating SOF metabolite *i.e.* GS-331007 (half-life 27 hours). Although it lacks anti-HCV activity *in vitro* this metabolite results from the dephosphorylation of the pharmacologically active analog nucleoside triphosphate GS-461203 produced by the extensive metabolization of SOF in the liver. Therefore, we assumed it is a marker of the patient exposure to phosphorylated SOF. Time to achieving undetectable HCV-RNA was confronted with mean DCV and SOF plasma concentrations and their sum measured at W2.

Results (1)

Table 1. Baseline characteristics of the 26 patients

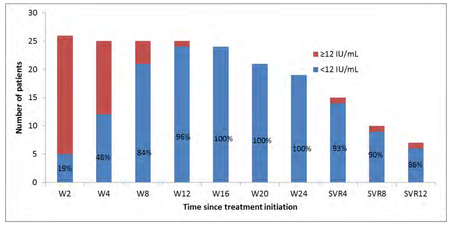
Male, n (%)	20 (77)
Age (median yrs, IQR)	52 (48-62)
Undetectable HIV load at D0, n (%)	25 (96)
CD4 T-cell count (cells/µL), median (IQR)	547 (290-1280)
Renal function (MDRD, ml.mn-1.1.73.M2), n (%)	
• Normal (≥90)	14 (54)
• Mild impairment (60-89)	11 (38)
• Moderate impairment (30-59)	1 (2)
Liver fibrosis score, n (%)	
• F3	5 (19)
• F4	21 (81)
Log_{10} HCV RNA (IU/ml), median (IQR)	6.06 (5.61-7.55)
HCV genotype, n (%)	
• 1a	15 (57)
• 1b	6 (23)
• 3a	3 (12)
• 4	2 (8)
Prior HCV treatment, n (%)	
• Naïve	4 (15)
• Interferon + ribavirin	17 (65)
• Interferon + ribavirin + telaprevir	3 (12)
• Interferon monotherapy	2 (8)
Prior HCV treatment response, n=22 (%)	
• Non-response	12 (55)
• Relapse	3 (14)
• Premature treatment discontinuation for adverse event	6 (27)
• Failure poorly characterized	1 (4)

Figure 1 . Distribution of antiretroviral regimens at baseline



Results (2)

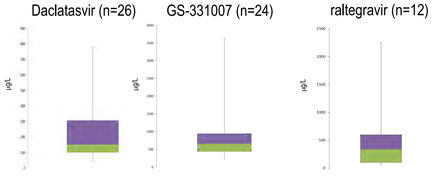
Figure 2 . Distribution of patients with HCV-RNA < 12 IU/mL at different time points



Four patients experienced grade 3 or 4 adverse events according to the French ANRS quotation [4]: severe anemia requiring blood transfusion (n=1); microcrystalline arthritis (chondrocalcinosis) (n=1); hepatocellular carcinoma (n=1) and relapse of hepatocellular carcinoma (n=1) one month after ending treatment requiring hospitalization.

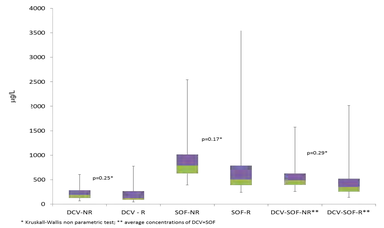
Results (3)

Figure 3 : Mean (± SD) daclatasvir, GS-331007, raltegravir C_{trough}



- *Mean darunavir C_{trough}: 3400 ± 1400 µg/L (n=6)*
- *Target C_{trough}: RAL 30-120 µg/L ; DRV 1500-4000 µg/L ; no recommended value for anti HCV drugs*

Figure 4 : W2 daclatasvir, GS-331007 and DCV+SGS-331007 C_{trough} among responders (R: HCV-RNA <12 IU/mL) and Non-respnders (NR) at W4



* Kruskall-Wallis non parametric test; ** average concentrations of DCV+SOF

Discussion

All-oral combination therapy with DCV plus SOF has been recently evaluated in patients with HCV mono-infection [5]. This open-label study randomly assigned 44 previously untreated patients with HCV genotype (G) 1 infection and 44 patients infected with HCV G2 or G3 to DCV at a dose of 60 mg orally once daily plus SOF at a dose of 400 mg orally once daily, with or without ribavirin, for 24 weeks. The study was expanded to include 123 additional patients with G1 infection who were randomly assigned to DCV plus SOF, with or without ribavirin, for 12 weeks (82 previously untreated patients) or 24 weeks (41 patients who had previous virologic failure with telaprevir or boceprevir plus peginterferon alfa–ribavirin). Once-daily oral DCV plus SOF was associated with high rates of sustained virologic response among patients infected with HCV G1 (98%), G2 (92%), or G3 (89%), including patients with no response to prior therapy with telaprevir or boceprevir. No data regarding the all-oral combination therapy with DCV plus SOF in HIV/HCV co-infection has been published. A phase III trial evaluating this combination therapy has been recently completed and is presented in this meeting [3]. Although preliminary and obtained in a limited number of patients, our data suggests that DCV plus SOF treatment is well-tolerated, safely co-administered with multiple ART regimens to HIV/HCV co-infected patients with extensive liver fibrosis, with an efficacy similar to that observed in HCV mono-infection.

Our data shows no large inter-individual variability of DCV C_{trough}, strengthening the data suggesting no dose adjustment requirement in patients with any degree of renal impairment or mild-to-severe hepatic impairment. DCV dose adjustment is required with strong CYP3A4 inhibitors such as HIV ritonavir boosted protease inhibitors or strong enzymatic inducers such as most NNRTIs [6]. Providing predefined DCV dose adjustment, our data does not suggest high impact of HIV drugs on DCV C_{trough}. On the other hand, our data suggests significant outliers for GS-331007 C_{trough}. Previous studies showed that while SOF AUC_{0-24} is highly impacted in patients with moderate and severe hepatic impairment compared to subjects with normal hepatic function, GS-331007 AUC_{0-24} is poorly affected. In contrast, mild and moderate renal impairment could affect the GS-331007 AUC [7]. In our study, renal function impairment did not appear to contribute to the significant outliers observed with GS-331007. SOF plus DCV combined therapy did not decrease raltegravir and darunavir C_{trough} below target values.

Finally, neither DCV, GS-331007 C_{trough} nor their sum were associated with W4 virologic response.

Conclusion

Interferon-free treatments for HCV are needed for HIV/HCV co-infected patients. Although preliminary, our data suggests that :

•DCV plus SOF treatment is well-tolerated and safely co-administered with multiple ART regimens to patients with extensive liver fibrosis. Grade 3 and 4 adverse events were noted in 4 patients and considered not drug related.

•The efficacy of DCV plus SOF therapy is similar to that observed in HCV mono-infection. No difference according to ART, INSTI, boosted PI, NNRTI-based and more complex regimens was observed.

Although limitations due to the design of our study, variability of DCV and GS-31007 trough concentrations did not appear to impact virologic efficacy of the combined therapy, neither the W4 response nor the sustained virologic response. This data should be further explored. On the other hand, DCV plus SOF therapy did not decrease raltegravir and darunavir C_{trough} below target values and more globally ART efficacy (data not shown).

All-oral combination of SOF plus DCV should be part of current therapeutic options in HIV/HCV co-infected patients with extensive liver fibrosis, as recommended in national and international guidelines.

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