Randomised clinical trial: sofosbuvir and ledipasvir in patients with transfusion-dependent thalassaemia and HCV genotype 1 or 4 infection

SOFOSBUVIR and LEDIPASVIR in transfusion-dependent thalassemia patients with HCV genotype 1 or 4 infection

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Summary

Background: Patients with thalassemia major depend on blood transfusions. In Italy, up to 80% of thalassemia patients bear HCV antibodies due to HCV contaminated transfusions before 1990. Thalassemia patients with HCV infection have high risk of developing HCC. Treatment based on Pegylated-IFN (Peg-IFN) and Ribavirin (RBV) was limited by relevant side effects.

Aim: To evaluate the impact of Sofosbuvir/Ledipasvir (SOF/LDV) fixed dose combination for 12 weeks without RBV, in patients with thalassemia major and HCV Genotype 1 or 4 (GT1/4).

Methods: Open label, historically controlled, nationwide multicentre study in thalassemia patients including naïve with cirrhosis and prior treatment failure without. SOF/LDV single pill was administered for 12 weeks to 100 patients of whom 16% had cirrhosis. Control group included 96 patients with comparable baseline characteristics treated with Peg-IFN/RBV. The primary end point was sustained virologic response at follow-up week 12 or 24 after IFN-free or Peg-IFN/RBV, respectively.

Results: In the study group, SVR was reported in 98% of patients (95% CI 95.3-100%). Cirrhotic as well as prior treatment failure achieved 100% SVR.

In the control group SVR was 47.9% (95% CI 37.9-57.9%). Adverse events including fatigue, headache, nausea, decrease in Hb or increase in ferritin levels were rare and significantly less common in the study than in the historical control group.

Conclusions: In conclusion, SOF/LDV for 12 weeks provides simple, highly effective and safe Peg-IFN/RBV free treatment for HCV GT1/4 thalassemia patients. EUDRACT number 2015-002401-1

Introduction

Regular blood transfusions and use of iron chelators have changed the prognosis of thalassemia major patients increasing survival especially for subjects born from 1980 to 1995 (1). Due to the improved survival, liver diseases related to HCV infection, including hepatocellular

carcinoma (HCC), emerged after cardiac diseases as the second risk factor associated with mortality in thalassemia (2). While in Italy, prevalence of thalassemia picks to 11% in Sardinia (7), the disease is highly prevalent in the Mediterranean area (8). Currently, in European Countries the risk of acquiring HCV by blood transfusion is 1.5-2 per 1 million donations, by contrast, the vast majority of patients who had received regular blood red cells transfusions before 1990 acquired HCV infection (3). It is therefore not surprisingly that the presence of HCV antibodies has been reported in 85% of multi-transfused thalassemia patients and the presence of HCV RNA in 70% of the HCV antibodies positive thalassemia major patients (4). Among HCV infected thalassemia patients the most common HCV genotype is genotype 1 (GT1).

In patients with chronic HCV infection, antiviral therapy reduces the risk of progression to cirrhosis, liver related complications and HCC (5), nevertheless, patients with concomitant systemic diseases, including hemoglobinopathies, are usually excluded from registration trials on direct acting antivirals (DAA). In the past, the use of Peg-Interferon (Peg-IFN) and ribavirin (RBV) in thalassemia patients with HCV infection was limited by both IFN and RBV side effects (9). In particular, RBV was associated with increase in blood transfusion requirements and consequent iron overload (10).

All oral IFN-free regimens based on DAAs able to block different regions of the viral genome represent the current standard of care for patients with HCV infection. LDV is a direct inhibitor of the viral region coding for HCV NS5A protein; like other first generation NS5A inhibitors, LDV has a low genetic barrier. Therefore, it is used in combination with SOF. LDV/SOF combination provides the shortest, single pill, once daily administration regimen for HCV GT1/4 and it is associated with Sustained virologic resposne (SVR) rates of 95% or higher in treatment naïve and of 94% in treatment experienced HCV infected patients (11,12). This treatment is expected not to be limited by drug-to-drug interactions with other medications usually taken by thalassemia patients. Given that, in Italy, the current reimbursement rules limit treatment of thalassemia patients to fibrosis stages of F3-F4, we evaluated SOF/LDV fixed dose combination in

patients with thalassemia major extending treatment beyond this criterion. SVR and tolerability were compared with those observed after Peg-IFN/RBV treatment in an historical control group treated at our Unit.

Patients and methods

Study design and population

One hundred and twenty-four patients with thalassemia major and HCV infection were screened. Twenty-four patients did not meet the inclusion criteria and did not start treatment. One hundred patients were prospectively treated. Eligible patients were at least 18 years old and had chronic HCV infection and thalassaemia major. Both naïve and treatment experienced were considered eligible. Treatment naïve included patients with compensated cirrhosis determined by the following: liver biopsy or transient elastography ≥12.5 KPa and APRI (AST/platelet ratio index>2)**[13]**. Liver stiffness measurements were considered reliable when based on at least 10 validated measurements, a success rate (the ratio of valid measurements to the total number of measurement) >60%, and an interquartile range (IQR, reflects variations among measurements) <30% of the median value (IQR/LSM ⩽30%)**[14].** Patients who failed a previous course of Peg-IFN and RBV treatment were excluded if cirrhotic and treated in accordance with the reimbursement criteria established by the Italian drug Agency (AIFA).

At screening, patients had the following laboratory parameters: ALT and AST ≤10 times UNL, total bilirubin ≤2 x ULN; creatinine clearance ≥ 40 mL/min; albumin ≥ 3 g/dl; INR≤1.5 ULN unless the patient was stable on anticoagulant regimen affecting INR; platelets ≥ 50.000/mm^3. Patients with concomitant HBV or HIV infection were excluded as well as patients with significant cardiac disease. Intrahepatic Iron concentration (LIC) (mg Fe/g/dry weight) was evaluated either invasively by liver biopsy or by Magnetic resonance imaging $MT2^*$ using the conversion formula **[15]**, or by Superconducting Quantum Interference Device (SQUID)**[16].**

All patients provided informed consent before undertaking the study procedures in the study arm.

Efficacy and safety of SOF/LDV were compared to Peg-IFN and RBV by evaluating SVR12 and SVR24 for either treatment respectively. Safety evaluation included RBV dose reductions cases or reductions in blood transfusion intervals in the study group and in 96 patients matched by age, gender and severity of liver disease treated at our centre from January 2009 to December 2011.

Treatment regimens

LDV 90 mg and SOF 400 mg as single pill fixed dose combination were administered once daily with food for 12 weeks to patients with or without cirrhosis without the addition of RBV. Patients in the historical control group had received Pegasys 180 mcg weekly plus RBV 1000 or 1200 mg based on body weight lower or higher than 75 Kg.

Study assessments

In the study arm, screening assessment included serum HCV RNA levels, HCV genotyping and IL28B genotyping in addition to standard laboratory clinical tests. Serum HCV RNA was measured by means of ABBOTT RealTime (ART) assay with a lower limit of quantification (LLQ) of 12 IU/ml and a lower limit of detection (LLOD) of 10-12 IU/ml. HCV genotype and subtype were determined with the use of Versant HCV genotype 2.0 Line Probe Assay (Innolipa). IL28B was performed by means of PCR amplification and sequencing of the rs12979860 single-nucleotide polymorphism **[17].**

Resistance testing was performed at the coordinating centre laboratory with the use of Sanger methods.

HCV NS3, NS5A and NS5B target regions were sequenced in all patients with relapse in the baseline sample and in sample obtained 4 weeks after relapse and at baseline in cases with discordant genotyping or subtyping results. The sequences from baseline samples were compared with those obtained after the virologic relapse to detect emergent resistance-associated variants.

Liver function was evaluated at baseline based on Child-Pugh and MELD scores.

The LIC threshold used to define the presence of iron overload was 1,2 Fe mg/g dry weight. Patients with ratio 3-7 had mild, 7 or higher had moderate and 15 or higher had severe iron overload [18].

HCV RNA was evaluated at baseline, and during treatment at week 4, 8, 12. After the end of treatment at week 4, 12 and 24. Biochemical laboratory parameters including ferritin levels were tested every four weeks on treatment and after 4 and 12 weeks after the end of treatment.

Study endpoints

The primary efficacy endpoint of the study was the rate of SVR which was defined as HCV RNA undetectable or ≤ LLOQ, 12 or 24 weeks after the end of therapy for patients treated with IFN free or IFN based regimens, respectively, in all patients who received at least one dose of SOF/LDV or Peg-IFN plus RBV. Post-treatment failure was defined as patients having HCVRNA ≥ LLOQ after previous undetectable results during treatment and relapse was defined as HCVRNA ≥ LLOQ during the post-treatment period in a patient with HCV RNA <LLOQ at the end of treatment.

Safety assessment

Safety data were collected during treatment every 4-weeks as well as 4 and 12 or 24 weeks after the end of treatment according to the IFN-free or IFN-based regimen. Adverse events, clinical laboratory tests, vital signs and concomitant medications intake were monitored. Electrocardiogram (ECG) recording was performed at baseline. Physical examination was done every 4-weeks during treatment as well as 4 and 12 or 24 weeks after the end of treatment.

Statistics

Statistical analyses were performed using SPSS vs 16.0. Continuous variables were reported as mean ± standard deviation or median and range. Categorical variables were reported as frequencies and percentages.

Student's T test was used for group comparisons of continuous variables when applicable. Otherwise Mann-Withney U test was applied. Group comparisons of categorical variables were performed using Chi squared or Fisher's exact test, as appropriate.

Ethics

The study was approved by the coordinating Site Ethic Committee and by each local ethics committee after the approval of the Italian drugs Agency (AIFA). The study was conducted in accordance with the Declaration of Helsinki.

Results

Study population

From January 2nd to September 2st 2016, 100 patients were screened, enrolled and treated at 5 sites in Italy. Baseline characteristics of patients treated with SOF/LDV are reported in Table 1. Fifty-seven patients were male, all were Caucasian and 63% were treatment naïve. Liver disease assessment showed cirrhosis in 16% of cases. In patients with cirrhosis, mean Child-Pugh score for cirrhosis mortality was A6; mean Model for End Stage Liver Disease (MELD), 7.

Mean baseline HCV RNA levels were 952.000 IU/ml (39-10.000.000). GT1 accounted for the vast majority of the infections (90 patients). Of GT1 infected patients, 9 had subtype 1a and three patients with contrasting subtype results were discovered by population sequencing, only after the start of treatment, to bear GT2 infection. GT4 was responsible of 7% of infections. In 4 additional cases a mixed genotype 1b/2a and in 1 further case a mixed genotype 1b/4 infection was detected. 98 patients who had previously received Peg-IFN and RBV at our Unit were matched by age ± 5

years, gender, HCV genotype and severity of liver damage with patients treated with SOF/LDV
Baseline characteristics of patients treated with Peg-IFN/RBV are shown in Table 1.
Among the SOF/LDV group, median transfusions interval at baseline was 18.9 days (17.6-20.1), among the IFN-based treatment group it was 19.5 days (18.3-20.5). Hb value before transfusion ranged between 9 and 10 g/dl regardless of the site.

Mild hepatic iron overload was demonstrated in 28% of patients treated with SOF/LDV and in 25% of patients in the historical control group, according with liver biopsy and/or MT2*results and/or SQUID.
Among patients treated with SOF/LDV, 48% received chelation treatment based on deferasirox alone (Exjade), 27% based on deferoxamine (Desferal), the remaining 25% received deferiprone (L1) alone or, in 6% of cases, in combination with deferoxamine. Among patients receiving IFN-based regimens, the corresponding percentages of different chelators were 34.3%, 29.9% and 36.4%.
Hormonal replacement treatment with the use of sexual hormones either testosterone or estroprogestin was reported by 19 patients due to hypogonadism.

Efficacy

SOF/LDV for 12 weeks resulted in an SVR12 of 98% (95% CI 95.26 to 100). The two virologic failures were both related to relapse, in one case at 4 and in the second case at 8 weeks post-treatment. Characteristics of patients who experienced a relapse in Table 2. Both patients were non cirrhotic and naïve, infected with GT1b. Plasma samples of these patients at baseline and four weeks after relapse were evaluated by population sequencing.
Overall, at week 4 of treatment, 81 patients had HCV RNA undetectable, while 9 patients had HCV RNA detectable but unquantifiable. All the patients had HCV RNA undetectable at week 8 of treatment and this result was maintained through the end of treatment and of follow up in all but two cases.

Among 96 patients who had received Peg-IFN and RBV in the historical control group, 46 achieved SVR24 (47.9%) (95% CI 37.92 to 57.91). SVR24 was attained in 45 of 82 (54.8) subjects without cirrhosis and in 1 of 14 with cirrhosis. Forty-two patients (43.8%) were HCV RNA undetectable at week 4 of treatment, 60.4% at week 8 and 72 at week 12 on treatment (75%). Two patients had a breakthrough. Twenty-two patients discontinued treatment due to RBV or Peg-IFN intolerance and were considered non responders (23%). Twenty-five had a relapse.

Viral resistance testing

At baseline no resistance associated substitutions were detectable in any of the 2 patients with virologic failure. After treatment failure, the two patients who had virologic failure had resistance associated substitution (RAS) in NS5A region. Patient 292-09 infected with subtype 1b developed Y93H but had P58S at baseline and 4 weeks after the virologic relapse. Patient 291-12 infected with genotype 1a developed L31I. (Table 3, Figure 1).

Safety

Overall 76% of patients treated with SOF/LDV developed adverse events. The most common adverse events among patients receiving SOF/LDV were headache (34%), fatigue (41%), and nausea (43%) (Table 3). No serious adverse events were registered. No patients discontinued treatment because of an adverse event.

No drug-to-drug interaction with chelation therapy including deferasirox, deferiprone or deferoxamine were observed. No changes in substitutive hormonal regimens were required.

In the historical control group, 23% of patients discontinued treatment due to RBV intolerance. No serious adverse events were registered. The most common adverse events reported in at least 2% of patients population in Table 3.

Changes in transfusions intervals, Hb and ferritin levels (baseline, on treatment and end of treatment)

Absence of RBV allowed the treatment of patients with thalassemia without the risk of increasing the number of blood transfusions and consequent increase in ferritin levels. Transfusions number during 12 weeks at baseline and at the end of treatment were compared between patients on SOF/LDV and patients who had received Peg-IFN/RBV. We calculated the mean transfusions number at baseline and during 12-week treatment period. They were 5.6±2.79 for patients receiving SOF/LDV and remained unchanged during treatment (5.5±2.79). The corresponding baseline values for patients treated with Peg-IFN/RBV were not different 5.21±1.47. However, a significant change during the first 12-week treatment was registered in the control group as transfusion number increased from 5.21±1.47 to 7.1±2.8 (P=0.004).

As shown in Fig. 2B, Hb levels declined significantly from 9.71 ± 0.73 g/dl to 8.81 ± 1.08 g/dl in the group of Peg-IFN/RBV treatment (p=0.0001), while remained substantially unchanged (10.44 ± 1.26 g/dl vs 10.63 ± 1.27 g/dl) in the group of patients who received SOF/LDV (p=0.059) Fig 2A. At follow-up week 12 mean Hb levels were 8.83 ± 1.15 g/dl in the group of Peg-IFN/RBV and 10.56 ± 1.31 g/dl in the group receiving SOF/LDV further confirming the benefit of this Peg-IFN/RBV free regimen.

Comparison of mean ferritin levels between baseline and end of treatment demonstrated that in the group of patients treated with SOF/LDV, ferritin levels declined from 758.69 ±688.03 ng/ml at baseline to 643.11 ± 607.98 ng/ml at the end of treatment (p=0.001).

By contrast a significant increase from 664.9 ± 484.87 to 1221 ± 866,46 ng/ml (p<0.0001) was observed in the group patients treated with Peg-IFN/RBV. Since HCV eradication itself might have an effect on serum ferritin levels, Peg-IFN/RBV treated patients were stratified by SVR status. Among non responder patients, mean ferritin levels increased from 667.42 ±505.23 ng/ml to 1202.02 ± 897.42 ng/ml, (p=0.006). Similar results were registered among responders as levels

increased from 672.23 ± 486.83 ng/ml at baseline to 1249.20 ± 871.74 ng/ml at post-treatment week 12 (p=0.0001). Therefore, the beneficial effect of antiviral treatment on ferritin was limited to patients receiving SOF/LDV and attributed to the tretment regimen rather than to the viral clearance.

Week 12 follow-up data

Liver stiffness was evaluated at the end of 12 weeks follow-up period. In the group of patients who achieved SVR12 after SOF/LDV, a significant decline from 7.93 ± 3.21KPa to 7.07 ±2.42 KPa was registered (p=0.0002). Among patients who received Peg-IFN/RBV mean liver stiffness increased from 8.7 ± 5.3 to 9.6 ± 7.1 (p<0.0001). The analysis of subgroups demonstrated among responders the absence of significant changes (6.6 ± 2.4 vs 6.4 ± 2.9, p= 0.51). At variance, a significant increase in liver stiffness was observed among non responders (10.5 ± 6.4 vs 12.4 ± 8.4, p=0.45). Whether the improvement in liver stiffness reflects reducing inflammation may be object of debate. Certainly, Peg-IFN/RBV free regimens have been associated with improvement in liver function.

Data on LIC are currently available only in a minority of patients treated with SOF/LDV. MT2* is usually performed at fixed intervals of 12-18 months in thalassemia patients and so far only 20% of patients in the group treated with SOF/LDV underwent the exam. Although a decline on LIC values was shown in this small subgroup, this data are very preliminary and need to be confirmed after a longer follow-up.

Finally, in the group of patients treated with SOF/LDV, ferritin levels were also evaluated at SVR12 and the significant decline from baseline was confirmed (769.28 ng/ml vs 649.96 ng/ml, p=0.001).

Discussion

The combination of SOF/LDV is the first singe pill fixed dose regimen approved by Food and Drug administration and European Medicine Agency to treat chronic HCV GT1 or GT4 infection **[11,12]**. In our cohort of thalassemia major HCV GT1 or 4 infected patients, this combination was associated with SVR rates of 98%. Further, concomitant drug use during therapy and in particular iron chelators did not show any impact on treatment completion or tolerability. SVR rates were similar to the rates observed in phase III, ION1 study even though inclusion criteria of our study allowed the inclusion of 33% previously treated patients **[11]**. These findings support a future recommendation of this regimen as the preferred treatment for HCV GT1 or 4 chronic infected thalassemia major patients.

Before the recent change in the label allowing in Europe the use of SOF/LDV for 12 weeks without RBV in cirrhotic patients, we demonstrated that in thalassemia naïve cirrhotic patients RBV is not required. Indeed, the study focused on patients naïve with compensated cirrhosis who were treated outside the European label recommending the use of RBV in addition to LDV for 12 weeks for all the patients with cirrhosis **[19]**, in keeping with AASLD recommendations instead **[20].** By contrast, thalassemia patients with cirrhosis and history of previous treatment failure were treated at each site within the Italian reimbursement recommendations for 24 weeks in parallel with this study **[21]**. Our results support the use of SOF/LDV for 12 weeks without ribavirin in naïve patients with cirrhosis as recently reported by the label. Remarkably, SVR12 rates were consistent with those reported in registration studies in subgroups of patients with compensated cirrhosis and with history of prior treatment failure. Moreover, the proportion of patients with SVR12 was similar across all different subgroups traditionally associated with lower SVR including subtype 1a **[11,12].**

Patients with thalassemia major were shown to have when HCV infected a greater risk of HCC **[22].** Indeed, due to the concomitant iron overload a prevalence of HCC 6 times higher than expected has been reported **[22,23]**. Moreover, an increased progression of fibrosis can be observed in subjects with thalassemia major and simultaneous HCV infection and iron overload, as compared

with patients with iron overload or HCV alone or without HCV and iron overload **[24,25]**. It is therefore extremely important to start HCV treatment as early as possible in these patients. So far, patients with thalassemia major and HCV have not been prioritized to IFN-free treatments. We offered a treatment option to all thalassemia patients regardless of the stage of fibrosis.

Interestingly, in 4 of our patients with mixed 1b/2a genotype infection as well as in 3 patients genotyped as 1b but resulting 2a by direct sequencing of baseline stored samples, SVR12 was 100%. These results are well in keeping with evidence generated in a phase II open label study showing SVR of 96% after 12 weeks of SOF/LDV treatment in patients with HCV GT2, despite an expected lower efficacy observed in vitro replicon system **[26].** This novel finding deserves real life evaluation in patients with genotype 2.

The baseline and post treatment samples of the two patients who developed the virologic failure were evaluated by population sequencing. NS5A RAS not detectable at baseline by population sequencing emerged in both cases at the time of relapse. This might be a reason for the virologic failure in 2 of our patients, in the absence of cirrhosis, previous history of IFN-based treatment and reported lack of adherence. Adherence of 98% was reported in the IFN-free arm (data not shown). We should anyway point out that in this study no drug concentration measurement had been planned. Therefore, adherence to treatment was evaluated only on the basis of pills count.

The regimen was safe and well tolerated. AEs and serious AEs were consistent with SVR12 rates reported in patients without thalassemia enrolled in phase II and III studies.
When the results of IFN-free treatment were compared with those attained in patients with similar proportion of cirrhosis or mild liver disease treated in the past with Peg-IFN and RBV, our data demonstrated that Peg-IFN/RBV free therapy is not only associated as expected with significantly higher SVR but, more importantly, with irrelevant side effects, lack of increases in the transfusion's number during treatment and consequent lack of significant ferritin levels increase.

Other regimens as the combination of elbasvir and grazoprevir recently approved by EMA have been investigated in thalassemia patients. In the C-EDGE IBLD study, 41 patients infected with HCV GT1 or 4 achieved 97,6% SVR with slightly lower SVR in GT 1a than in GT1b **[27].** Although these results appear promising, it should be considered that the use of protease inhibitors metabolized by CYP P450 might expose patients with thalassemia who receive a number of concomitant medications to an increased risk of drug to drug interactions.

Potential limitations of this study may be lack of centralized laboratory and histological assessments. However, the different sites laboratories used as outcome undetectable HCV RNA rather than HCV RNA <LLQ. Moreover, in the majority of patient's liver stiffness rather than liver biopsy was used to establish severity of liver damage and predefined criteria were established on the basis of IQR and a minimum of 80% rate of valid measurements. Finally, since the end point of SVR is not subject to bias, the open label design of this study is not likely to represent a bias. Follow up studies are planned to investigate in the long term potential benefits associated with HCV eradication in liver or not liver related outcomes in patients with beta thalassemia major. According with currently available liver stiffness and ferritin results, an improvement in the overall morbidity can be expected in thalassemia patients after Peg-IFN and RBV free successful treatment.

In conclusion, SOF/LDV FDC for 12 weeks provides simple, highly effective treatment for patients with thalassemia major and concomitant HCV GT1 or 4 infections. It appears an effective and safe regimen in naïve patients with cirrhosis regardless of the chelators adopted. Our results also suggest high efficacy of this combination for 12 weeks in GT2 infected patients. This regimen may represent a decisive treatment to reduce morbidity and mortality in developing countries where both the risk of HCV infection related to blood transfusion and the prevalence of thalassemia continue to represent a concern for larger numbers of subjects.

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Table 1 Baseline characteristics of patients treated with SOF/LDV or Peg-IFN/RBV

	SOF/LDV No.100, (%)	PEG-IFN/RBV No.96, (%)	P value
Mean Age, years (range)	43.58 (42.4-47.8)	36.69 (28.1-50.2)	0.08
Male sex, n (%)	57 (57.0)	52 (54.2)	0.88
BMI kg/m2 (range)	22.87 (17.1-33.4)	23.71 (16.8-34.9)	0.07
Genotype 1/4/2/undetermined	90/7/3/0	74/7/6/9	0.007
Subtype 1a	9	6	0.59
Treatment history naive	63 (63.0)	61 (61.0)	0.65
Liver stiffness, Mean KPa (range)	8.2 (4.1-24)	8.8 (3.7-29.1)	0.12
Cirrhosis, n (%)	16 (16.0)	14 (15.0)	1.0
Mean HCV RNA, log10 IU/ml ±SD	952.000±1.839.590	142.000.000±2.856.475	0.049
Mean ALT levels U/l	80.09±80.49	106.9±100.9	0.001
Mean AST levels U/l	47.45±32.75	55.93±42.51	0.043

Mean baseline PLT count u/l	454510±190312	438860±217996	0.42
PLT <100.000 u/l, n (%)	6 (5.9)	5 (5.2)	1.0
Albumin <3.5 g/dl	12	11	1.0
Mean glucose levels	100.45 (69-434)	95.68 (61-272)	0.96
Diabetes mellitus, no (%)	13 (13.0)	8	0.62
GFR < 80 ml/min	20	Not available	-
Mean baseline ferritin levels (ng/ml)	758.69 (92-4222)	644.99 (100-4578)	0.21
IL28B CC	19 (31.0)	33 (35.4)	0.30
Desferoxamine Deferiprone Deferasirox	27 (27.0) 25 (25.0) 48 (48.0)	35 (36.4) 28 (29.1) 33 (34.3)	0.11
Iron accumulation Moderate/severe Mild Absent	 28 (28.0) 17 (17.0) 55 (55.0)	 25 (26.0) 23 (23.9) 48 (50.0)	0.47
Mean Liver Iron Concentration	4.28±4.65	3.18±2.53	0.17

Table 2. Characteristics of patients with relapse in SOF/LDV arm

	Genotype	Baseline HCV RNA (IU/ml)	Time of HCV RNA reappearance	NS5 RAVS At baseline	NS5 RAVs 4 weeks after relapse
male	1a	56347	4	None	L31I
female	1b	3750000	8	Q30L, P58S	Y93H, P58S

Table .3 Adverse events and laboratory abnormalities with exclusion of anemia

	LDV/SOF	Peg-IFN/RBV	P value
Serious adverse events	0	1	0.49
Adverse events leading to treatment discontinuation	0	18	0.0001
Increased ALT on treatment	3	13	0.004
Increased GGT on treatment	5	20	0.001
Adverse events in more than 2% of pts between or within each regimen Arthralgia Fever	 3 None	 1 16	 0.63 0.0001
Erythematous rash	None	5	0.62
Astenia	2	91	0.005
Nausea	18	9	0.098
Headache	14	7	0.168

Fatigue	27	22	0.50