Safety and Efficacy of Antiviral Therapy of Chronic Hepatitis C in Chronic Kidney Disease and Hemodialysis Patients

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ABSTRACT

Background and Aims: To assess the efficacy and tolerability of sofosbuvir-based antiviral therapy for viral hepatitis C (HCV) patients with chronic kidney disease and on maintenance hemodialysis.

Methods: We retrospectively reviewed all treated patients with HCV from January 2015 to November 2020. They were treated either with standard Interferon/Ribavirin or with Sofosbuvir combined to Daclatasvir or to Ledipasvir. We evaluated the sustained virologic response at 12 weeks (SVR12). Data were analyzed using SPSS 20.00.

Results: Out of 61 patients, the mean age of our patients was 56.8±12.56 years and 42.6% were males. Six patients had eGFR< 60 ml/mn/1.73 m² (9.8%) and 26 patients were on maintenance hemodialysis (42.6%). The majority had genotype 1 and overall SVR12 was 70.1% with a rate of 75% in the Sofosbuvir-regimen subgroup. The adverse events were minor. On multivariate analysis, genotype, viral load and rapid virologic response were independent factors that significantly predicted treatment success.

Conclusion: Sofosbuvir-based regimen appears to be safe and efficous in patients with chronic kidney disease and on maintenance hemodialysis, especially in countries with limited resources.

Keywords: Chronic kidney disease, hemodialysis, hepatitis C virus, Sofosbuvir, sustained virologic response.

I. INTRODUCTION

Epidemiological data indicate that about 170 million people have chronic viral hepatitis C infection (HCV) [1, 2]. The global prevalence of anti-HCV has been estimated at 2% among adults and 1.6% for all ages [3]. In Africa, over 28 million people are chronically infected with HCV with varying prevalence from one Africa country to another [3]. The overall prevalence in Morocco of HCV infection in the general population is 1.58% [4]. The prevalence of HCV infection among Moroccan dialysis patients was reported to be high and varied widely between hemodialysis centers from 11 to 91% [5]. Hemodialysis is among the most important risk factors for HCV and is associated with increased morbidity.
and mortality because of both liver and cardiovascular disease [3]. These data emphasize the importance of antiviral therapy in HCV-infected patients with impaired renal function especially in patients with stage 4-5 chronic kidney disease (CKD) [6], [7]. During the interferon-era of antiviral therapy, disappointing few HCV-positive CKD and end stage renal disease (ESRD) patients have been offered antiviral treatment [8], [9]. Significant progress has been made in the last decade in the treatment of HCV with high levels of sustained virologic response (SVR) even in the CKD population [10], [11]. Direct-acting antiviral therapies (DAAs) have revolutionized the management of HCV, transforming it into a curable infection [12]. All patients with advanced CKD can now be treated with FDA-approved DAA regimens that are interferon (INF) free [12]. Only sofosbuvir (SOF), daclatasvir (DAC) and ledipasvir (LED) are available in Morocco and cost-accessible to patients. SOF is a prodrug that is phosphorylated in the active metabolite GS-461203, both cleared by the kidneys [9], [13]. It is not approved for patients with eGFR<30 ml/mn/1.73 m². However, off-label use of SOF in advanced renal failure has been reported [12], [14]. Accordingly, the aim of this study is to evaluate the efficacy and safety profile of SOF-based in CKD and hemodialysis patients with chronic HCV infection.

II. PATIENTS & METHODS

A. Patients

We retrospectively reviewed medical records of all adult patients with chronic HCV infection treated at University Hospital Center of Marrakesh from January 2015 to November 2020. The study population included all treated HCV-positive ESRD on maintenance dialysis at five hemodialysis centers in Marrakesh. Exclusion criteria were patients with hepatitis B or HIV co-infection and patients lost to follow-up. Demographic, clinical, adverse events, and laboratory data were collected prior to initiation of treatment, throughout the treatment period and the post-treatment follow-up until the determination of SVR at 12 weeks (SVR12). The diagnosis of HCV infection was documented by HCV RNA through PCR and genotyping. HCV RNA level ≥ 800000 IU/ml was used as cut-off value HCV RNA level [15], [16]. Fibrosis was evaluated by liver biopsy and/or transient elastography with a median score above 12.5 kPa being considered as consistent with cirrhosis (on a scale of 1.5 of 75.0 kPa). Laboratory tests included serum creatinin and urea, complete blood count, serum aminotransferase enzymes, gamma glutamyl transferase and albumin. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation [17]. Three groups of patients were determined on the basis of eGFR: group 1 (eGFR ≥ 60 ml/mn/1.73 m²), group 2 (eGFR <60 ml/mn/1.73 m²) and group 3 (hemodialysis).

Treatment history divided patients into treatment naïve and treatment experienced. HCV RNA by PCR was checked at 4 and 12 weeks during treatment period and at 12 weeks post treatment to define sustained virologic response (SVR12).

B. Statistical Analysis

Data were analyzed using SPSS statistical software (version 20.0). Quantitative data were expressed as mean±SD or median (min-max) and qualitative data as numbers with percentages. We used the Mann-Whitney U non-parametric test for non-normally distributed continuous variables and the student’s t-test for normally distributed variables. Categorical variables were compared using Pearson’s χ² test. The level of significance was set at p<0.05. Significant variables were included in multivariate logistic regression.

III. RESULTS

A. Baseline Characteristics

There were 61 patients who met the inclusion criteria. Of these, 26 patients were on chronic maintenance hemodialysis. The mean age of our patients was 56,8±12,56 years, and 42.6% were males, 23% had diabetes and 50.8% had antecedents of arterial hypertension.

The main risk factors of viral transmission were blood transfusion (n=21; 34,4%), surgery (n=23; 37,7%), informal dental care (n=28; 45,9%), invasive procedures (n=2; 3%,) scarification (n=10; 16,39%), tattooing (n=5; 8,2%) and high-risk sexual relation (n=5; 8,2%).

The diagnosis of viral hepatitis C was made by serological systematic screening in all hemodialysis patients. The majority of patients had genotype 1 (n=30; 49,2%), especially genotype 1b (n=27; 44,26%) and 9 patients had fibrosis grade 4 (14,8%).

Our study population included 29 patients with a baseline eGFR≥60 ml/mn/1,73 m² (47,5%), 6 patients with eGFR<60 ml/mn/1,73 m² (9,8%) and 26 patients on maintenance hemodialysis (42,6%).

B. Virologic Response

In total, 19 patients (31,1%) received standard interferon/ribavirin (INF/RBV), 38 patients (62,3%) received sofosbuvir and daclatasvir (SOF/DAC) and 4 patients (6,6%) received sofosbuvir and ledipasvir (SOF/LED). The majority of patients who were treated with INF-regimen had eGFR ≥ 60 ml/mn/1,73 m² while 2 patients had eGFR < 60 ml/mn/1,73 m² and 4 patients were on maintenance hemodialysis. Among the sofosbuvir (400 mg once daily)-based regimen group, 16 patients had eGFR≥60 ml/mn/1,73 m², 4 patients had a eGFR between 30 and 60 ml/mn/1,73 m² and 22 patients were on maintenance hemodialysis. Demographic, clinical, laboratory characteristics and treatment regimen of the patients are presented in Table 1.

Among the 61 patients, virologic response was evaluated in 58 patients, 3 hemodialysis patients stopped definitely their treatment due to adverse events. A rapid virologic response (RVR) was observed in 21 patients (36,2%) and a sustained virologic response at 12 weeks (SVR12) was achieved in 41 patients (70,1%). In the subgroup SOF-based regimen, SVR12 was 75% and in the subgroup INF-based treatment, SVR12 was 58,82% without a significant difference (p=0,201), but at the price of a longer duration of treatment with INF (INF: 48 weeks in 57,9% of cases and 24 weeks in42,1% of cases vs SOF : 12 weeks in 63,1% of cases and 24
weeks in 36.9%; p=0.000), SVR12 were higher in patients who achieved a RVR (p=0.013), in patients with a low viral load (p=0.002) and in the case of genotype 2 or 4 (p=0.000). On multivariate analysis, genotype 2 or 4, low viral load and rapid virologic response were independent factors that significantly predicted treatment success. Treatment results according to patients’ characteristics are provided in Table 2.

### Table 1: Characteristics of Study Subjects (N=61)

| Characteristics | Group 1 | Group 2 | Group 3 | p  |
|-----------------|--------|--------|--------|----|
| Age; years old (mean±SD) | 59±11.38 | 57±12.17 | 54.31±13.86 | 0.390 |
| Male sex (n, %) | 10 (16.4%) | 1 (1.6%) | 15 (24.6%) | 0.088 |
| BMI ≥ 30 Kg/m² (n, %) | 6 (9.8%) | 2 (3.3%) | 0 (0%) | 0.023 |
| Antecedents: Diabetes (n, %) | 4 (6.6%) | 3 (4.9%) | 7 (11.5%) | 0.129 |
| Arterial hypertension (n, %) | 5 (8.2%) | 5 (8.2%) | 21 (34.4%) | 0.000 |
| Cardiac disease (n, %) | 2 (3.3%) | 1 (1.6%) | 7 (11.5%) | 0.278 |
| Alcohol consumption (n, %) | 2 (3.3%) | 0 (0%) | 1 (1.6%) | 0.735 |
| Neoplasia (n, %) | 3 (4.9%) | 1 (1.6%) | 1 (1.6%) | 0.496 |
| Polymedication (n, %) | 8 (13.1%) | 5 (8.2%) | 24 (39.3%) | 0.000 |
| History of treatment: Treatment naïve | 23 (37.7%) | 3 (4.9%) | 22 (36.1%) | 0.174 |
| Treatment experienced | 6 (9.8%) | 3 (4.9%) | 4 (6.6%) | 0.829 |
| Viral status: RNA ≥ 800,000 IU/ml (n, %) | 8 (13.1%) | 11 (1.6%) | 0.998 | 0.013 |
| Genotype (%): G1 | 5 (8.2%) | 12 (19.7%) | 0.112 |
| G2 | 14 (23%) | 9 (14.8%) | 0.413 |
| G4 | 0 (0%) | 5 (8.2%) | 0.015 |
| Fibrosis (n, %): F0 | 21 (34.4%) | 4 (6.6%) | 20 (32.8%) | 0.192 |
| F1 | 3 (4.9%) | 2 (3.3%) | 0.709 |
| F2 | 5 (8.2%) | 0 (0%) | 0.335 |
| F3 | 3 (4.9%) | 2 (3.3%) | 0.345 |
| F4 | 12 (19.7%) | 11,29±1,36 | 0.496 |
| Hemoglobin (g/dl): Group 1 | 12.94±2.81 | 11,1±1,5 | 0.829 |
| Group 2 | 17 (29.3%) | 11,29±1,36 | 0.784 |
| Group 3 | 28 (48.3%) | 11,29±1,36 | 0.591 |
| Leucocytes (ele/mm³): Group 1 | 7216±462 | 46,6% | 0.709 |
| Group 2 | 52 (8.2%) | 46,6% | 0.591 |
| Group 3 | 36,9% | 46,6% | 0.335 |
| Platelets (ele/mm³): Group 1 | 36,9% | 46,6% | 0.335 |
| Group 2 | 36,9% | 46,6% | 0.335 |
| Group 3 | 36,9% | 46,6% | 0.335 |
| Albumin (g/dl) | 36,07±2,99 | 43,75±47,6 | 0.335 |
| Hepatic enzymes (mean±SD): ALAT (IU/ml) | 52,68±37,55 | 43,75±27,7 | 0.335 |
| ASAT (IU/ml) | 43,07±31,16 | 32,16±2,99 | 0.335 |
| GGT (IU/ml) | 13(21,3%) | 52±35,31 | 0.335 |
| Albumin | 0,013 | 2,17±0,29 | 0.335 |

### Table 2: Treatment Results According to Patients’ Characteristics

#### Sustained virologic response at 12 weeks (SVR12)

| Characteristics | Yes (N, %) | Non (N, %) | p  | OR [IC,95%] | p  |
|-----------------|-----------|------------|----|-------------|----|
| Age categories (years old, %): | | | | | |
| 25-45 | 5 (8.6%) | 3 (5.2%) | 0.709 |
| 46-65 | 24 (41.1%) | 8 (13.8%) | | | |
| 66-85 | 12 (20.7%) | 6 (10.3%) | | | |
| Male sex (%) | 17 (29.3%) | 6 (10.3%) | 0.662 |
| BMI ≥ 30 Kg/m² (%) | 5 (8.6%) | 3 (5.2%) | 0.584 |
| Antecedents: Diabetes | 8 (13.8%) | 5 (8.6%) | 0.411 |
| Arterial hypertension | 19 (32.8%) | 9 (15.5%) | 0.647 |
| eGFR (%): ≥ 60 ml/min/1.73m² | 18 (31%) | 11 (19%) | 0.343 |
| < 60 ml/min/1.73m² | 5 (8.6%) | 1 (1.7%) | | | |
| Hemodialysis | 18 (31%) | 5 (8.6%) | | | |
| Genotype (%): G1 | 13 (22.4%) | 15 (25.9%) | 0.129 |
| G2 or G4 | 28 (48.3%) | 2 (3.4%) | | | |
| Viral load (%) | | | | | |
| ≥ 800000 IU/ml | 5 (8.6%) | 9 (15.5%) | 0.002 |
| < 800000 IU/ml | 36 (62.1%) | 8 (13.8%) | | | |
| RVR (%) | 19 (32.8%) | 2 (3.3%) | 0.002 |

#### C. Adverse Events

Among the 61 patients, 7 patients temporarily suspended their treatment and 3 hemodialysis patients stopped it definitely due to adverse events (INF: one case with psychiatric disorder and one case of anemia; SOF: one case of anemia). The major observed adverse effects were asthenia (47.5%) and flu-like syndrome (13.1%) (Table 3). Six patients had a drop of eGFR ≥ 10 ml/min/1.73 m² (SOF: 5 cases with a baseline eGFR ≥ 60 ml/min/1.73 m² in 4 patients and a eGFR < 60 ml/min/1.73 m² in one patient; INF: one patient with a baseline eGFR < 60 ml/min/1.73 m²).
TABLE 3: ADVERSE EVENTS IN STUDY SUBJECTS

| Adverse events                  | Treatment regimen (N) |
|---------------------------------|-----------------------|
|                                 | SOF-based regimen     | INF-based regimen |
| Asthenia                        | 12                    | 17                 |
| Flu-like syndrome               | 0                     | 8                  |
| Weight loss                     | 0                     | 5                  |
| Pruritus                        | 4                     | 1                  |
| Nausea                          | 5                     | 1                  |
| Psychiatric disorders           | 0                     | 1                  |
| Anemia                          | 1                     | 6                  |
| Neutropenia                     | 0                     | 4                  |
| Thrombopenia                    | 0                     | 4                  |
| Hyperuricemia                   | 0                     | 3                  |
| Thyroid dysfunction             | 0                     | 3                  |
| Elevated transaminase level     | 0                     | 1                  |

IV. DISCUSSION

Treatment of chronic HCV infection in patients with CKD is associated with a number of challenges. Until recently, treatment possibilities for advanced CKD and hemodialysis patients were limited to INF/RBV-based therapies which were poorly tolerated with cure rates of 32% on average [12], [18], [19]. The advent of direct antiviral-acting (DAAs) has dramatically improved the management of HCV. Several DAAs regimens showed high efficacy and safety in patients with advanced CKD and ESRD, including elbasivir/ grazoprevir, ombitasvir/dasabuvir/paritasvir/ritonavir and glecaprevir/pibrentasvir [20], [21]. However, considering the non-availability and high-cost of these DAAs in developing countries, several clinical trials have evaluated the safety and efficacy of sofosbuvir-based therapies in patients with severe renal impairment even if sofosbuvir is not approved for patients with eGFR<30 ml/ min/1.73 m² [12].

A meta-analysis summarizing DAAs use in advanced renal failure reported that several combinations of DAAs containing sofosbuvir were effective with 89% SVR12 and an excellent tolerability [12], [14]. Several controlled studies have evaluated the use of sofosbuvir in more severe renal dysfunction, identifying dose adjustments in advanced renal disease and hemodialysis [22], [23], [24]. In cases where novel DAAs are not available and the use of sofosbuvir is an option, a full dose of sofosbuvir (400 mg/day) seems more appropriate than a half dose or a full dose on alternate day [25]. Mandhwani et al reported 133 hemodialysis patients treated with full dose sofosbuvir-based regimens (group INF: SOF-INF-RBV/ group DAC: SOF-DAC-RBV): the majority of patients had genotype 1 and achieved a SVR12 in 100% of group INF and 97% of group DAC and minor adverse events were observed (anemia in 43.6% and elevated alanine transaminases in 8.1%) [26]. In our study, genotype 1 was the most common and the rate of treatment success was 75.6% in the subgroup SOF-based regimen with no need for dose adjustment and no major adverse event.

The HCV-Target, a longitudinal real-world observational study of 1893 patients who received treatment with multiple sofosbuvir-based regimens, concluded that overall SVR12 was 82-83% across all patient groups with higher rates of worsening renal dysfunction and serious adverse events among patients with eGFR< 45 ml/ min/1.73 m² [27]. However, other clinical trials did not report significant alteration of kidney function with either full dose of SOF every other day or half dose daily [16], [28].

In a real-life experience study, Medeiros et al showed that patients with kidney dysfunction did not experience significant changes in renal parameters after full dose SOF-based therapy in patients with either eGFR ≥ 45 ml/ min/1.73 m² or eGFR< 45 ml/ min/1.73 m² [24]. Our results were in accordance to this study, as we did not notice any significant alteration of renal function in non-hemodialysis patients.

With regard to the predictive factors associated with sustained virologic response, various host and viral variables have been identified. Buti et al reported that reduced response rates occurred more frequently in the case of HCV genotype 3 or 1a, elevated viral load, treatment-experienced patients, advanced cirrhosis, poor compliance or premature drug discontinuation [29].

In our study, high viral load, HCV genotype 1 and rapid virologic response were independent positive predictors of SVR12.

In summary, treatment with SOF-based regimen was effective and tolerable in HCV-infected patients with advanced chronic kidney disease and on maintenance hemodialysis in our study. Although it is preferable to use sofosbuvir-free regimen in this population, this drug may be safely prescribed under close monitoring when we have limited choices to treat patients with renal impairment.

REFERENCES

[1] Mohd Hanafiah K, Groeger J, Fluxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013 ; 57: 1333-42.
[2] Lee MH, Yang HI, Yuan Y, L'Italian G, Chen CJ. Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol 2014; 20: 9270-80.
[3] Dav MA, El-Bouzedi A, Ahmed MO, Daa AA, Agnan MM. Hepatitis C virus in North Africa: An emerging threat. The scientific World Journal 2016, 1-11.
[4] Baha W, Foullous A, Desi et al. Prevalence and risk factors of hepatitis B and C virus infections among the general population and blood donors in Morocco. BMC Public Health 2013. Vol 13, article 50.
[5] Abdelaal BOM, Tausif D, Samir A, Saad M. Hepatitis C viral prevalence and seroconversion in Moroccan hemodialysis units: eight year follow up. Journal of Medical Diagnostic Methods 2013. 2: 141.
[6] Bhamidimari MR, Czul F, Peyton A, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease. J Hepatol 2015; 6: 763-765.
[7] Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation and treatment of hepatitis C in chronic kidney disease. Kidney International 2008; 73:S1-S99.
[8] Goodkin DA, Binder B, Gillespie B, Robinson BM, Jadoul M. Hepatitis C infection is very rarely treated among hemodialysis patients. Am J Nephrol 2013; 38: 405-412.
[9] Pagan J, Ladino M, Roth D. Treating hepatitis C virus in dialysis patients: How, when, and why?. Seminars in Dialysis 2018; 1-7.
[10] Lanini S, Easterbrook PJ, Zumla A, Ippolito G. Hepatitis C: global epidemiology and strategies for control. Clin Microbiol Infect 2016; 22: 833-8.
[11] Fabrizi F, Messa P. Treatment choices for hepatitis C in patients with kidney disease. Clin J Am Soc Nephrol 2018; 13: 793-5.
[12] Davis ML, Chute DF, Chung RT, Sise ME. When and how can nephrologists treat hepatitis C virus infection in dialysis patients?. Seminars in Dialysis 2017; 1-11.
[13] Ladino M, Pedraza F, Roth D. Hepatitis C virus infection in chronic kidney disease. J Am Soc. Nephrol 2016: 27: 2238-2246.
[14] Li T, Qu Y, Guo Y, Wang Y, Wang L. Efficacy and safety of direct-acting antiviral combination for patients with stage 4-5 chronic kidney disease: a meta-analysis. Liver Int 2017; 37: 974-981.

[15] Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol 2012; 60: 2082-2089.

[16] Shin HP, Park JA, Burman B, Kozarek RA, Siddique A. Efficacy and safety of sofosbuvir-based regimens for treatment in chronic hepatitis C genotype 1 patients with moderately impaired renal function. Clinical and Molecular Hepatology 2017; 23: 316-322.

[17] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3:1-150.

[18] Koenig P, Vogel W, Umlauf F, et al. Interferon treatment for chronic hepatitis C virus infection in uremic patients. Kidney Int 1994; 45: 1507-1509.

[19] Fernandez J, Rendo P, Pino L. A double-blind controlled trial of recombinant interferon-α2b in haemodialysis patients with chronic hepatitis C virus infection and abnormal aminotransferase levels. J Viral Hepatitis. 1997;4: 113-119.

[20] Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SUFFER study): a combination phase 3 study. Lancet 2015; 386(10003): 1537-1545.

[21] Henson JB, Sise ME. The association of hepatitis C infection with the onset of CKD and progression into ESRD. Seminars in Dialysis 2018;1:1-11.

[22] Maruyama A, Partovi N, Yoshida EM, Erih SR, Azalgara VM, Hussaini T. A review of direct-acting antivirals for the treatment of hepatitis C in patients with advanced chronic kidney disease. Nephrol Dial Transplant 2017; 32:35-41.

[23] Fabrizi F, Martin P, Messa P. New treatment for hepatitis C in chronic kidney disease, dialysis, and transplant. Kidney Int 2016; 89: 988-994.

[24] Medeiros T, Rosario NF, Saraiva GN, Andrade TG, Silva AA, Almeida JR. Renal safety after one year of sofosbuvir-based therapy for chronic hepatitis C: A brazilian «real-life» study. J Clin Pharm Ther 2018;1:7.

[25] Constancio NS, Ferraz MLG, Martins CTB, Kraychete ACK, Bitencourt PL, do Nascimento MM. Hepatitis C in hemodialysis units: diagnosis and therapeutic approach. Braz J Nephrol 2019; 41(4): 539-549.

[26] Mandhvari R, Hanif FM, Lail G, Luck NH, Khalid MA, ul Haque MM, Laeq SM, Aziz T. Use of sofosbuvir based regimen in patients with end-stage renal disease and chronic hepatitis C; an open label, non-randomized, single arm, single center study from Pakistan. Gastroenterol Hepatol Bed Bench 2020; 13(2): 141-146.

[27] Saxena V, Koraishy FM, Sise ME, Lim JK, Chung RT, et al. Sfaety and efficacy if sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int 2016; 36: 807-816.

[28] Cornprost M, Denning JM, Clemons D, Marbury TC, Alcorn H, Smith WP, et al. The effect of renal impairment and end stage renal disease on the single-dose pharmacokinetics of PSI-7977. J Hepatol 2012; 56: 5433.

[29] Buti M, Riveiro-Barciela M, Esteban R. Management of direct antiviral agent failures. J Hepatol 2015; 63: 1511-1552.