ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2018 November 27; 10(11): 785-891

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Monthly Volume 10 Number 11 November 27, 2018

World Journal of Hepatology

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Monthly Volume 10 Number 11 November 27, 2018

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World Journal of Hepatology (*WJH*) is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/1948-5182/editorialboard.htm

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PUBLICATION DATE
November 27, 2018

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Hepatology

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World J Hepatol 2018 November 27; 10(11): 856-866

DOI: 10.4254/wjh.v10.i11.856

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfected patients

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Author contributions: All the authors contributed to this work

Supported by Inserm-ANRS (French National Institute for Health and Medical Research - ANRS/France REcherche Nord and Sud Sida-hiv Hépatites).

Institutional review board statement: The study was approved by the Institutional Review Board Ile de France Ⅲ, Paris, France

Informed consent statement: A written informed consent was obtained from each participant to the study.

Conflict-of-interest statement: Dominique Salmon has been speaker and received invitation to conferences by Gilead, Abott, and MSD. Laurent Alric received grant and personal fees from MSD, Gilead, Abbvie, Janssen and BMS outside the submitted work. Christine Katlama received consultancy fees and/or travel grants from MSD, Janssen, ViiV outside the submitted work. Karine Lacombe personal fees from Gilead, personal fees from Janssen, personal fees from Abbvie, personal fees from Merck outside the submitted work. Philippe Morlat received personal fees and non-financial support from GILEAD, Janssen, MSD and ViiV Health Care outside the submitted work. Gilles Peytavin received travel grants, consultancy fees or study grants from pharmaceutical companies including Abbvie, Bristol-Myers Squibb, Gilead sciences, Janssen, Merck and ViiV Healthcare outside the submitted work. Eric Rosenthal received personal fees from Gilead and Abbvie and travel grants, consultancy fees from Gilead, Abbvie, MSD and BMS outside the submitted work. Philippe Sogni received personal fees and non-financial support from Gilead, BMS, MSD Abvie outside the submitted work. Caroline Solas received personal fees from Gilead, Abbvie, Janssen, MSD and ViiV Healthcare outside the submitted work. Linda Wittkop reports grants from ANRS during the conduct of the study; personal fees from Janssen, Gilead, MSD, outside the submitted work. Other authors had nothing to declare.

STROBE statement: The guidelines of the STROBE Statement have been adopted. The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Unsolicited manuscript

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Received: June 15, 2018
Peer-review started: June 15, 2018
First decision: July 9, 2018
Revised: September 10, 2018
Accepted: October 10, 2018
Article in press: October 10, 2018
Published online: November 27, 2018

Abstract

AIM

To describe factors associated with treatment failure and frequency of resistance-associated substitutions (RAS).

METHODS

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfected patients starting a first direct-acting antiviral (DAA) regimen before February 2016 and included in the French ANRS CO13 HEPAVIH cohort were eligible. Failure was defined as: (1) non-response [HCV-RNA remained detectable during treatment, at end of treatment (EOT)]; and (2) relapse (HCV-RNA suppressed at EOT but detectable thereafter). Sequencing analysis was performed to describe prevalence of drug class-specific RAS. Factors associated with failure were determined using logistic regression models.

RESULTS

Among 559 patients, 77% had suppressed plasma HIV-RNA < 50 copies/mL at DAA treatment initiation, 41% were cirrhotic, and 68% were HCV treatment-experienced. Virological treatment failures occurred in 22 patients and were mainly relapses (17, 77%) then undefined failures (3, 14%) and non-responses (2, 9%). Mean treatment duration was 16 wk overall. Post-treatment NS3, NS5A or NS5B RAS were detected in 10/14 patients with samples available for sequencing analysis. After adjustment for age, sex, ribavirin use, HCV genotype and treatment duration, low platelet count was the only factor significantly associated with a higher risk of failure (OR: 6.5; 95%CI: 1.8-22.6).

CONCLUSION

Only 3.9% HIV-HCV coinfected patients failed DAA regimens and RAS were found in 70% of those failing. Low platelet count was independently associated with virological failure.

Key words: Human immunodeficiency virus; Hepatitis C virus; Direct-acting antiviral; Treatment virological failure; Resistant associated mutations

Core tip: In co-infected human immunodeficiency virus-hepatitis C virus (HCV) patients, after adjustment for age, sex, ribavirin use, HCV genotype and treatment duration, low platelets count was the only factor significantly associated with a higher risk of failure.

Salmon D, Trimoulet P, Gilbert C, Solas C, Lafourcade E, Chas J, Piroth L, Lacombe K, Katlama C, Peytavin G, Aumaitre H, Alric L, Boué F, Morlat P, Poizot-Martin I, Billaud E, Rosenthal E, Naqvi A, Miailhes P, Bani-Sadr F, Esterle L, Carrieri P, Dabis F, Sogni P, Wittkop L; ANRS CO13 Hepavih study group. Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfected patients. *World J Hepatol* 2018; 10(11): 856-866 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i11/856.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i11.856

INTRODUCTION

The treatment of hepatitis C virus (HCV) infection had been revolutionized with the recent development of direct-acting antiviral (DAA) combinations. Cure rates of over 90%, similar to those in HCV monoinfected patients, can now be achieved in human immunodeficiency virus (HIV)/HCV coinfected patients. This has been documented in clinical trials[1-5] as well as in real-life cohorts[6-9]. For the few patients failing treatment, resistance-associated substitutions (RAS) can emerge and emerging resistant strains appearing at viral rebound are a consequence rather than a cause of failure[10,11].

The real causes of failure to all-oral DAA regimens can be multiple. Several social and medical factors can jeopardize treatment adherence. Some first-generation regimens may not be optimal to treat difficult cases of hepatitis C, such as decompensated cirrhosis or genotype 3 HCV infection. In rare circumstances, especially for genotype 1a viruses, baseline mutations in the non-structural-5A (*NS5A*) gene can preexist in the viral species before treatment introduction and may have a potentially deleterious impact on sustained virological response (SVR)[12]. Drug-drug interactions between DAA and ARV therapy or other commonly prescribed medications in HIV/HCV coinfected patients are frequent and can decrease drug levels, thereby reducing the efficacy of therapy. Finally, adverse events, although rare with new DAA combinations, can occur and lead to treatment interruption and thus to treatment failure.

We aimed to describe the characteristics of patients failing first-line DAA treatment in the real-life French nationwide ANRS CO13 HEPAVIH cohort of HIV/HCV coinfected patients. Furthermore, we described the emergence of clinically relevant RAS to DAA classes upon DAA treatment failure, and report pharmacological drug monitoring results. Finally, we identified factors associated with the occurrence of virological treatment failure.

MATERIALS AND METHODS

Study population

The ANRS CO13 HEPAVIH cohort (ClinicalTrials.gov Identifier: NCT03324633) is a national multi-centre prospective hospital-based observational study of patients coinfected with HIV and viral hepatitis C that received approval by an Institutional Review board [Comité de Protection des Personnes (CPP) Ile de France Ⅲ, Paris, France].

All patients included in the cohort gave their consent

for study participation. In addition, patients from the 29 centers participating in the ANRS CO13 HEPAVIH cohort, who weren't included in the cohort but who gave their consent for specific follow-up during and after DAA treatment, were also eligible. For this sub-study, patients were included if they had started an all-oral DAA-based regimen before January 2016 (3 mo treatment), February 2016 (2 mo treatment) or October 2015 (6 mo treatment). Patients who participated in completed and published clinical trials were included in the analysis. We did not include patients who were participating in an ongoing clinical trial (including those completed but not yet published), patients who were treated with combinations including Peg-interferon (PegIFN), or with the sofosbuvir (SOF) + ribavirin (RBV) combination. Patients with premature treatment interruption for intolerance or death were also excluded because we were specifically interested in a virological outcome. The DAA regimen was at the discretion of the patient's physician[13-15].

Data collection and definitions

The following data were collected prospectively by each participating center, using an eCRF: Age, sex, risk factors for both HIV and HCV infections, HCV genotype, previous anti-HCV treatment, HIV-related characteristics, start and end dates of DAA treatment, initial doses of anti-HCV and anti-HIV drugs, any changes during follow-up, and HCV-RNA at each time point [baseline, week (W)2, W4, W8, W12 if treatment duration was 24 wk, EOT, follow-up W4 (FU-W4) and FU-W12]. Virological treatment failures were categorized as: (1) Non-response: HCV-RNA never undetectable during treatment; (2) Relapse: HCV-RNA undetectable at EOT and then detectable within the following 12 wk; and (3) Undefined failure: HCV-RNA unknown at end of treatment (EOT) and positive thereafter, without premature discontinuation of treatment. Cirrhotic status was based on liver biopsy (METAVIR fibrosis stage F4), liver stiffness $\geqslant$ 12.5 kPa (FibroScan®; Echosens, France), a FibroTest® value $\geqslant$ 0.75 (Biopredictive, France) or physical and biological signs of end-stage liver disease, as previously published[16,17].

Sequencing analysis

Patients with virological treatment failure, who provided specific consent for HCV genotype testing and who had HCV-RNA > 1000 IU/mL at the sequencing time point were included for HCV testing. Prevalence of drug class-specific RAS was evaluated at failure. The HCV NS3, NS5A and/or NS5B domains were amplified by reverse transcriptase nested polymerase chain reaction (PCR) using genotype and subtype-specific PCR primers to ensure successful amplification of the target gene(s). PCR products were purified and analyzed by population sequencing using an automated sequencer (ABI-3500xL Dx). The cutoff frequency for detecting variants with Sanger sequencing was approximately 15%. Sanger-derived sequences were aligned with Clustal_W, version 1.74 (Conway Institute UCD, Dublin, Ireland). NS3, NS5A and NS5B RAS were defined as clinically relevant when inducing > 10-fold resistance to DAA[13,18-20].

Drug concentrations

Plasma drug concentrations for DAA and RBV were collected, when available, for patients included in the cohort as part of routine therapeutic drug monitoring performed in several centers. Drug concentrations were measured using liquid chromatography coupled with the tandem mass spectrometry method[21]. Data were considered interpretable if concentrations were determined at steady-state and information regarding the time of the last drug intake was available.

A suboptimal concentration was defined as below the 2 μg/mL threshold for RBV[22,23], and when concentrations were below the reported expected range for DAA[24-27].

Statistical analysis

We included all patients who met the inclusion criteria, as described in the study population section. Variables are described as number and percentages, or median and IQR [or mean (SD)], as appropriate. Patient characteristics are reported upon initiation of DAA treatment. The Wilcoxon-Mann-Whitney test and Fisher's exact test were used to compare quantitative and qualitative variables between groups, respectively. Factors associated with virological treatment failure were determined using logistic regression models. In order to identify new independent predictors of virological treatment failure, we systematically adjusted for a fixed set of potential confounders based on literature reports. The following variables were thus forced in all models: age, sex, RBV use, and prescribed treatment duration[28]. We then tested the following variables in the model containing the forced variables: HCV genotype (3 *vs* others), cirrhosis (Yes *vs* No), severe cirrhosis (Yes *vs* No, and defined by a B or C or an elastometry value $\geqslant$ 20 kPa), plasma HIV-RNA (detectable *vs* undetectable), and platelet count (< 100 Giga/L *vs* $\geqslant$ 100 Giga/L). The effect of RBV on virological treatment failure and other potential factors was assessed by a marginal structural model (MSM) in order to consider a potential indication bias for the prescription of RBV. Sensitivity analyses, including patients with premature treatment discontinuations for intolerance/death, were also performed. The statistical methods of this study were reviewed by Linda Wittkop from Bordeaux Population Health Research Center, Bordeaux. SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

RESULTS

General characteristics at DAA initiation

Among 877 patients treated with DAA-combination, 559 met the inclusion criteria and were included in the analysis (318 were not included for the following reasons: Treatment with PegIFN (n = 30), inclusion

Table 1 Patient characteristics at treatment initiation according to virological response

	Overall (n = 559)	SVR (n = 537)	Virological treatment failure (n = 22)	P value
Male sex	431 (77)	414 (77)	17 (77)	0.985
Age (yr)	52 (49-56)	52 (49-56)	53 (51-57)	0.586
CD4 (/mm^3) (n = 557)	618 (426-850)	619 (429-861)	527 (346-704)	0.040
Undetectable HIV-RNA (n = 558)	486 (87)	469 (88)	17 (77)	0.186
ARV treatment	549 (98)	527 (98)	22 (100)	1.000
PI[1]	127 (23)	122 (23)	5 (23)	
NNRTI[2]	98 (18)	95 (18)	3 (14)	
II[3]	204 (37)	197 (37)	7 (32)	
Others	120 (22)	113 (21)	7 (32)	
Active tobacco consumption (n = 263)	153 (58)	148 (58)	5 (71)	0.703
Active alcohol consumption (n = 266)	135 (51)	132 (51)	3 (43)	0.719
Active drug consumption (n = 257)	7 (3)	7 (3)	0 (0)	1.000
HCV genotype (n = 558)				0.475
1 without precision	26 (5)	24 (5)	2 (9)	
1a	232 (42)	221 (41)	11 (50)	
1b	64 (12)	64 (12)	0 (0)	
2	6 (1)	6 (1)	0 (0)	
3	62 (11)	60 (11)	2 (9)	
4	165 (30)	158 (30)	7 (32)	
5	1 (0)	1 (0)	0 (0)	
6	2 (0)	2 (0)	0 (0)	
Cirrhosis (n = 555)	209 (38)	200 (38)	9 (41)	0.748
Child Pugh, if cirrhosis (n = 189)				0.537
A	172 (91)	165 (91)	7 (88)	
B/C	17 (9)	16 (9)	1 (12)	
FIB-4 (n = 405)	2.1 (1.4-3.7)	2.1 (1.4-3.7)	3.3 (1.9-7.3)	0.313
FIB-4 > 3.25 (n = 405)	120 (30)	113 (29)	7 (50)	0.132
Elastometry (kPa) (n = 115)	9 (6-14)	9 (6-14)	10 (6-17)	0.942
Elastometry ⩾ 12.5 kPa (n = 115)	32 (28)	30 (27)	2 (50)	0.309
Elastometry ⩾ 20 kPa (n = 115)	17 (15)	16 (14)	1 (25)	0.478
HCV treatment history				0.570
Naïve	210 (38)	203 (38)	7 (32)	
Pretreated	349 (62)	334 (62)	15 (68)	
HCV viral load (log_{10} IU/mL) (n = 558)	6.09 (5.59-6.51)	6.09 (5.59-6.51)	6.04 (5.72-6.49)	0.886
Prothrombin rate (n = 298)	99 (89-100)	99 (89-100)	92 (82-100)	0.116
Prothrombin rate < 85% (n = 298)	54 (18)	50 (17)	4 (40)	0.087
Platelets (Giga/L) (n = 408)	171 (131-219)	171 (133-219)	148 (97-184)	0.168
Platelets < 100 Giga/L (n = 408)	57 (14)	51 (13)	6 (43)	0.007
Albumin (g/L) (n = 301)	41 (38-44)	41 (38-44)	42 (37-45)	0.939
Albumin < 35 g/L (n = 301)	26 (9)	24 (8)	2 (25)	0.146
DAA-combination				NA[5]
SOF + DCV ± RBV[4]	240 (43)	231 (43)	9 (41)	
SOF/LDV ± RBV	271 (49)	261 (49)	10 (46)	
SOF + SMV ± RBV	26 (4)	23 (4)	3 (14)	
Others[4]	22 (4)	22 (4)	0 (0)	
Mean (SD) DAA treatment durationa	16 (6)	15 (5)	16 (6)	

Results are presented as number (as percentages in brackets) or median (IQR in brackets) unless stated otherwise. [1]PI was boosted in 98 patients with SVR and in five patients with treatment failure; [2]NNRTI molecule was rilpivirine in 60 patients with SVR and three with failure, and was efavirenz in 25 patients with SVR; [3]II molecule was raltegravir in 153 patients with SVR and four patients with failure, and was dolutegravir in 38 patients with SVR and two with treatment failure; [4]Initial doses of DCV were 30, 60, 90 mg/d in respectively 57, 159 and 21 patients. The dose was unknown for the five other patients; [5]NA: not applicable, no formal statistical comparison was performed as the prescription of the DAA regimen was chosen by each patient's physician. SVR: Sustained virological response; ARV: Antiretroviral; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; II: Integrase inhibitor; DAA: All-oral direct-acting antiviral; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; LDV: Ledipasvir; SMV: Simeprevir.

in an ongoing clinical trial (n = 2), treatment after the period of analysis (n = 190), no available treatment result (n = 32), treatment with SOF + RBV (n = 60), premature treatment interruption for intolerance (n = 3), and one patient died while on treatment). Mean treatment duration was 16 wk overall (15 wk in patients who failed DAA therapy and 16 wk in those with SVR). The characteristics of the 559 patients are summarized in Table 1.

Virological treatment failure

The virological treatment failure rate was 3.9% (95%CI: 2.5-5.9). Overall, 22 virological treatment failures were observed: Two non-responses, 17 relapses and three undefined virological treatment failures (HCV-RNA unknown at EOT). By univariate analysis (Table

Table 2 Adjusted logistic regression for factors associated with virological treatment failure

Covariables	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	*P* value	OR (95% CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
	n = 538		*n* = 538		*n* = 526		*n* = 395	
Age at treatment initiation (per 10 yr)	1.2 (0.6-2.4)	0.58	1.3 (0.7-2.5)	0.48	1.2 (0.6-2.4)	0.53	1.6 (0.7-4.0)	0.29
Ribavirin *vs* no ribavirin	1.0 (0.3-3.0)	0.97	1.1 (0.3-3.2)	0.93	1.0 (0.3-3.0)	0.97	1.4 (0.4-5.5)	0.61
Male sex *vs* female	1.0 (0.4-2.8)	0.98	0.9 (0.3-2.7)	0.92	1.0 (0.3-2.8)	0.97	0.8 (0.2-2.7)	0.69
Treatment duration 24 wk *vs* 12 wk	0.4 (0.1-1.4)	0.15	0.5 (0.2-1.5)	0.21	0.4 (0.1-1.4)	0.16	0.2 (0.0-1.0)	0.05
Platelet count < 100 Giga/L *vs* ⩾ 100							6.5 (1.8-22.6)	0.004
Cirrhosis *vs* no cirrhosis	1.4 (0.5-3.9)	0.51						
HIV-RNA detectable *vs* undetectable			2.1 (0.7-5.9)	0.17				
Severe cirrhosis *vs* no severe cirrhosis					2.1 (0.4-10.3)	0.35		
HCV genotype 3 *vs* others							0.9 (0.1-7.5)	0.91

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

1), patients with virological treatment failure had a significantly lower CD4 cell count (median 527 cells/mm^3) compared to patients with SVR (619 cells/mm^3; P = 0.040). They also more frequently had a platelet count below 100 Giga/L (P = 0.007) and a trend for more frequently having a prothrombin time < 85% (40% *vs* 17%, P = 0.087) and albumin < 35 g/L (25% *vs* 8%, P = 0.146). They also had a non-significant trend for less frequent HIV-RNA suppression (77% *vs* 88%, P = 0.186).

Factors associated with treatment failure

In adjusted models (Table 2), platelet count < 100 Giga/L was significantly associated with a higher probability of virological treatment failure (Model 4). However, clinical cirrhosis status (Model 1), severe cirrhosis status (Model 3) or blood albumin (data not shown) were not associated with a higher probability of failure. Neither HIV-RNA (Model 2) nor CD4 cell count (data not shown) were associated with virological treatment failure. In addition, in the model containing platelet count, a prescribed treatment duration of 24 wk was associated with a lower risk of virological treatment failure (Model 4). RBV use was not associated with outcome in adjusted logistic regression models, and this result was confirmed by an analysis using MSMs (data not shown).

Sensitivity analyses, including patients with premature treatment discontinuations for intolerance/death, showed similar results (data not shown).

HCV resistance at virological treatment failure

The results of RAS analysis in the 14 patients with virological treatment failure, in whom either mutation NS3, NS5A or NS5B could be sequenced, are presented in Table 3. Almost three quarters of patients with available data (10/14; 71%) had at least one detectable RAS at the time of virological treatment failure. In patients receiving an NS5A inhibitor-based regimen, 55% (6/11) had NS5A RAS upon virological treatment failure. Common substitutions detected at failure included Q30R/H, 30E, 58D and/or Y93C/N, all found in patients with HCV genotype 1. In patients treated with daclatasvir (DCV) and an available NS5A RAS result (n = 5), four patients developed resistance to DCV. Furthermore, among six treated with ledipasvir (LDV) with available NS5A RAS result, two developed resistance to LDV. Overall, in all patients with available genotype (n = 14), six (43%) presented at least one NS5A RAS, leading to a high level of resistance to NS5A inhibitors (> 10-fold resistance). In patients receiving NS3 protease inhibitors, 2/2 patients with available data had NS3 RAS upon virological treatment failure. The substitutions detected at failure were 80K, 170T, 174N and 168V, leading to a high level of resistance to most protease inhibitors.

Multiple RAS conferring a higher level of resistance were detected in three (21%) patients, including two with NS3 + NS5A RAS and one with NS3 + NS5A + NS5B RAS. These three patients were previously treated with PegIFN + RBV and were exposed to NS5A inhibitors but not NS3 inhibitors.

Pharmacological data

Nine of the 22 (41%) patients who had DAA therapy failure had measurements of DAA and/or RBV concentration at W2 or W4 of treatment, seven of which were interpretable. Among these seven patients, suboptimal concentrations were reported in two (29%). These low concentrations concerned either DCV (in a patient treated with SOF + DCV, whose ARV treatment was rilpivirine + raltegravir), or RBV (in a patient treated with SOF/LDV + RBV who was taking rilpivirine + dolutegravir).

DISCUSSION

In this cohort of HIV/HCV coinfected patients, who were treated with an interferon-free DAA regimen with or without RBV, we report a low virological treatment failure rate of 3.9%. Our results are similar to those observed in clinical trials[28] or previous real-world studies of HIV/HCV coinfection[6,7]. Most of these virological treatment failures were due to relapse (77%) followed by non-response (9%), while 14% were due to undefined virological treatment failures (HCV-RNA unknown at EOT).

Due to very high rates of SVR, it has been difficult to identify factors associated with virological treatment failure of DAA in real-world studies, and no study to date has focused on HIV coinfection. In studies of HCV

Table 3 Resistance-associated substitution results in 14 patients with virological treatment failure for whom sequencing was performed in routine care

Pat	HCV treatment history	Treatment received	HCV genotype		Cirrhosis	ARV treatment	RAS		
			Before treatment	After treatment			NS3	NS5A	NS5B
A	Pretreated	SOF + SMV 12 wk	1a	1a	Yes	II	Q80K, I170T, S174N	Abs	Abs
B	Pretreated	SOF + SMV 12 wk	1a	1a	Yes	II	D168V	Abs	Abs
C	Pretreated	SOF/LDV 12 wk	4	4a	No	PI	Abs	Abs	Abs
G	Pretreated	SOF/LDV + RBV 12 wk	4	4d	No	Others	Abs	Abs	Abs
H	Pretreated	SOF + DCV 10 wk[3]	4	4	No	Others	Abs	ND	Abs
I	Naive	SOF/LDV 12 wk	1a	1a	No	PI	Abs	Abs	Abs
J	Pretreated	SOF/LDV 12 wk	1a	1a	No	Others	ND	Y93C	Abs
L	Naive	SOF + DCV 13 wk[2]	1a	1a	Yes	NNRTI	Q80K	Abs	Abs
M	Pretreated	SOF/LDV 12 wk	4	4a	No	PI	ND	Abs	A421V, M414L
N	Pretreated	SOF/LDV + RBV 12 wk	1a	1a	Yes	II	A168V	30E, 58D	Abs
P	Pretreated	SOF + DCV + RBV 12 wk[1]	1a	1a	No	PI	Abs	Y93N	Abs
Q	Pretreated	SOF + DCV + RBV 24 wk[1]	1a	1a	No	Others	T54S	Q30R	Abs
R	Pretreated	SOF + DCV 24 wk[2]	1a	1a	Yes	II	Q80K	Y93C	Y448H
W	Pretreated	SOF + DCV 24 wk[1]	1	1a	Yes	II	Abs	Q30H	Abs

[1]Initial dose of DCV: 30 mg/d; [2]Initial dose of DCV: 60 mg/d; [3]Initial dose of DCV: 90 mg/d. Pat: Patient; ARV: Antiretroviral; RAS: Resistance-associated substitution; NS3: Non-structural-3; NS5A: Non-structural-5A; NS5B: Non-structural-5B; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; LDV: Ledipasvir; SMV: Simeprevir; ND: Not done; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; II: Integrase inhibitor; Abs: No RAS found.

monoinfected patients, however, several factors have been found to be associated with virological treatment failure: severity of cirrhosis (assessed by presence of ascites), low albumin, low platelet count/high total bilirubin[29-35], male sex[30,31], and the preexistence of baseline RAS[34,36].

In our study, we found that low platelet count was significantly associated with a higher rate of virological treatment failure. It is likely that low platelet count is a surrogate marker of cirrhosis, since we found an association between low albumin levels and low PT time by univariate analysis. However, we failed to observe a significant relationship between severe cirrhosis and failure. This might be due to the fact that in cases of severe cirrhosis, physicians adapted the treatment to each complex situation by extending the duration or by adding RBV (76% of the patients with Child Pugh B or C cirrhosis received treatment of 24 wk duration *vs* 29% of the other patients in our study), and this might be explained by unreported events of decompensation.

In the first randomized phase 3 clinical trials, which assessed the efficacy and safety of DAA, decompensated cirrhosis was an exclusion criterion, which precluded the possibility of assessing this factor as a potential predictor of failure. More recently, several trials have clearly demonstrated that patients with Child Pugh B or C cirrhosis and those with genotype 3 infection have a lower rate of SVR with DAA alone and need the addition of RBV. This was the case for the SOF/LDV combination and for a combination[37,38] of velpatasvir/SOF[39].

We observed a trend (by univariate analysis only) toward a higher rate of detectable HIV-RNA in patients with virological treatment failure *vs* in those with SVR (P = 0.19). This might reflect suboptimal adherence, with patients who are non-compliant for their HIV treatment while possibly also non-adherent to their HCV treatment. Nonetheless, this result did not remain significant by multivariable analysis and thus may also simply reflect a biased estimate.

Moreover, among seven patients with failure and interpretable pharmacological data, suboptimal blood concentrations of DAA were measured in two of them. These results could reflect different situations (drug interactions, suboptimal dosing errors, suboptimal adherence) and warrant both further investigation and wider-scale assessment of pharmacological data. Regarding RAS in our study, we did not determine pretreatment RAS and we cannot exclude the possibility that some failures may be due to pre-existing RAS. However, at a population level, the effects of baseline RAS in *NS5A*, although not rare, are minimal[10,36,40,41]. This prompted EASL experts[18,20] to recommend that genotyping should not be performed for naïve patients but instead considered when retreatment is anticipated with a *NS5A* inhibitor regimen in patients who have previously failed NS5A treatment.

In most of our patients who failed DAA-treatment, RAS was investigated. We found RAS in 50% of those failing NS5A-based therapy and in the two patients failing NS3, but no major RAS S282T to NS5B. This high prevalence of *NS5A* and -3 RAS failure in our study confirms the EASL recommendation to evaluate HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) if resistance testing is available, as these analyses can guide decisions for further treatment[18,20].

There are several limitations to this study. Firstly, since the study was an observational cohort, our results must be interpreted with caution, since treatment

prescriptions were dependent on drug availability (with variations over time) and known efficacy with regards to HCV genotypes. Those results were obtained with second generation DAA (LDV, DCV, elbasvir/grazoprevir), and those results may not be entirely applicable to the newer, pangenotypic regimens such as velpatasvir/SOF or pibentasvir/glecaprevir. Our analysis is limited by the small number of subjects with virological treatment failure, and thus likely has limited power to identify all potential risk factors. All patients with virological treatment failure could not be explored by genotyping to investigate the emergence of RAS due to the need to obtain patient consent. Furthermore, baseline genotyping was not available routinely, since this test is not recommended in France for treatment-naïve patients. Finally, Sanger sequencing was used for the detection of RAS, which may not be sensitive enough to detect minor populations of RAS (< 15%). The strengths of our study include prospective data collection with regular monitoring and high quality data.

In conclusion, our study identified that low platelet count is associated with a higher probability of DAA failure. This parameter likely reflects hepatic insufficiency, and our results are concordant with previously published findings on HCV monoinfected patients. We also speculate that some degree of low adherence could explain some cases of failure, since suboptimal drugs levels were observed in 29% of the cases that could be explored, and HIV viral load was often detectable in patients with virological treatment failure to DAA. This study confirms the very low rate of treatment failure with all-oral DAA in HIV/HCV coinfected patients, as well as the high risk of the emergence of non-structural NS3 or NS5A RAS in patients with virological DAA failure.

ARTICLE HIGHLIGHTS

Research background

In human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfection, all-oral direct-acting antiviral (DAA) regimens achieve virological cures in > 95% of patients.

Research motivation

Risk factors for failure are mainly related to severity of cirrhosis in HCV monoinfected patients, but are unknown in the population of HIV HCV coinfected patients. We wanted to know whether additional factors related to non-adherence or HIV status could be involved in the occurrence of failures. We believed that identifying the risk factors for failure would allow for the adaptation of treatment to patients with higher risk of failure.

Research objectives

The main objectives were to determine the risk factors for virological treatment failure to DAA in HIV/HCV coinfected patients and to describe the frequency of RAS.

Research methods

HIV/HCV coinfected patients who started the first DAA regimen before February 2016 and who were included in the French ANRS CO13 HEPAVIH cohort were eligible. Failure was defined as: i) Non-response (HCV-RNA remained detectable during treatment, at end of treatment (EOT)), ii) relapse (HCV-RNA suppressed at EOT but detectable thereafter). Sequencing analysis was performed to describe prevalence of drug class specific RAS. Factors associated with failure were determined using logistic regression models.

Research results

Research findings: Among 559 patients, 77% had suppressed plasma HIV-RNA < 50 copies/mL at DAA treatment initiation, 41% were cirrhotic, and 68% were HCV treatment-experienced. Virological treatment failures occurred in 22 patients and were mainly relapses (17, 77%) then undefined failure (3, 14%) and non-responses (2, 9%). Mean treatment duration was 16 wk overall. Post-treatment NS3, NS5A or NS5B RAS were detected in 10/14 patients with samples available for sequencing analysis. After adjustment for age, sex, RBV use, HCV genotype and treatment duration, low platelet count was the only factor significantly associated with a higher risk of failure (OR: 6.5; 95%CI: 1.8-22.6); Contributions to the field: In HIV/HCV coinfected patients, the risk factors of failure were more related to the severity of cirrhosis than to HIV immunovirological status or non-adherence issues. Problems that remain to be solved: It remains to be determined whether the low platelet count associated with a higher probability of failure reflects the severity of cirrhosis.

Research conclusions

In our study of HIV/HCV patients receiving all-oral DAA, only 3.9% HIV-HCV coinfected patients failed DAA regimens. RAS were found in 70% of those failing. Low platelet count was independently associated with virological failure. We think that this low platelet count reflects the severity of cirrhosis.

Research perspectives

As the treatment failure number is low, it would be useful to build international collaborations and gather data for several cohorts in order to gain significance power. The results obtained with first generation all-oral DAA could be compared with the newer, pangenotypic drug regimen.

ACKNOWLEDGMENTS

Patients of the ANRS CO13 HEPAVIH Cohort. Scientific Committee: Salmon D (co-Principal Investigator), Wittkop L (co-Principal Investigator), Sogni P (co-Principal Investigator), Esterle L (project manager), Trimoulet V, Izopet J, Serfaty L, Paradis V, Spire B, Carrieri P, Valantin MA, Pialoux G, Chas J, Poizot-Martin I, Barangue K, Naqvi A, Rosenthal E, Bicart-See A, Bouchaud O, Gervais A, Lascoux-Combe C, Goujard V, Lacombe K, Duvivier C, Vittecoq D, Neau D, Morlat P, Bani-Sadr F, Meyer L, Boufassa F, Dominguez S, Autran B, Roque AM, Solas C, Fontaine H, Costagliola D, Piroth L, Simon A, Zucman D, Boué F, Miailhes P, Billaud E, Aumaître H, Rey D, Peytavin G, Petrov-Sanchez V, Pailhe A. Clinical Centres: APHP Cochin, Paris (Médecine Interne et Maladies Infectieuses: Salmon D, Usubillaga R; Hépato-gastro-entérologie: Sogni P; Anatomo-pathologie: Terris B; Virologie: Tremeaux P); APHP Pitié-Salpétrière, Paris (Maladies Infectieuses et Tropicales: Katlama C, Valantin MA, Stitou H; Hépato-gastro-entérologie: Benhamou Y; Anatomo-pathologie: Charlotte F; Virologie: Fourati S); APHP Pitié-Salpétrière, Paris (Médecine Interne: Simon A, Cacoub P, Nafissa S); APHM Sainte-Marguerite, Marseille (Service d'Immuno-Hématologie Clinique: Poizot-Martin I, Zaegel O, Laroche H; Virologie: Tamalet C); APHP Tenon, Paris (Maladies Infectieuses et Tropicales: Pialoux G, Chas J; Anatomo-pathologie: Callard P, Bendjaballah F; Virologie: Le Pendeven C); CHU Purpan, Toulouse (Maladies Infectieuses et

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P- Reviewer: Abushady EAE, Bouare N, Lee GH, Milovanovic T
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