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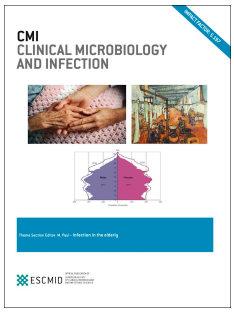

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CATHEGORY: Viral Hepatits

Optimal efficacy of interferon-free HCV retreatment after protease inhibitors failure in real life

RUNNING TITLE: Real-life retreatment of HCV PI failures

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ABSTRACT

Objectives: First-generation protease-inhibitors (PIs**)** had suboptimal efficacy in GT-1 patients with advanced liver disease, and those who failed may need urgent retreatment. Our objective was to analyze the real-life efficacy of interferon (IFN)-free retreatment after PI-failure, and the role of genotypic-resistance-testing (GRT) in guiding retreatment choice.

Methods: In this multi-center observational study, patients retreated with IFN-free regimens after first-generation PI-failure (telaprevir-boceprevir-simeprevir) were included. Sustained-virological-response (SVR) was evaluated at week 12 of follow-up. GRT was performed by population-sequencing.

Results: After PI-failure, 121 patients (cirrhotic=86.8%) were retreated following 3 different strategies: A) with "GRT-guided" regimens (N=18); B) with "AASLD/EASL recommended, not GRT-guided" regimens (N=72); C) with "Not recommended, not GRT-guided" regimens (N=31). Overall SVR rate was 91%, but all 18 patients treated with "GRT-guided" regimens reached SVR (100%), despite heterogeneity in treatment-duration, PI- and RBV-inclusion, *vs*. 68/72 patients (94.4%) receiving "AASLD/EASL recommended, not GRT-guided" regimens. SVR was strongly reduced (77.4%) among the 31 patients who received a "not recommended, not GRT-guided regimen" (p-trend<0.01).

Among 37 patients retreated with a PI, SVR rate was 89.2% (33/37). Four GT-1a cirrhotic patients failed an option (C) simeprevir-containing treatment; 3/4 had a baseline R155K NS3-RAS. All 7 patients treated with a paritaprevir-containing regimens reached SVR, regardless treatment-duration and performance of a baseline-GRT.

Conclusion: retreatment of PI-experienced patients can induce maximal SVR rates in real-life. Baseline-GRT could help to optimize retreatment strategy, allowing also PIs to be reconsidered when chosen after a RASs evaluation.

INTRODUCTION

The frequent development of NS3 resistance associated substitutions (RASs) at failure limits retreatment options with protease inhibitors (PIs) for patients who previously failed a PI containing regimen. To avoid cross-resistance both AASLD and EASL recommend to use a combination of an NS5A-inhibitor plus sofosbuvir (SOF)(1, 2), without performing any baseline genotypic-resistance-testing (GRT). However, in retreatment settings, GRT can be clinically helpful in providing additional confidence for NS5A-inhibitors use, accounting for possible presence of natural NS5A-RASs(1, 3, 4), and in evaluating alternative 2nd line regimens besides those suggested by guidelines.

Very few reports are available on real-life retreatment of PI-experienced patients(5-7), and on the use, and utility, of baseline HCV-GRT in this setting.

METHODS

We analyzed the efficacy of several IFN-free retreatment strategies chosen for 121 patients with cirrhosis (86.8%) or advanced fibrosis (median[IQR] liver-stiffness: 10[10-12] kPa) who previously failed a PI (boceprevir, N=51; telaprevir, N=69; simeprevir[SIM], N=1) plus pegylated-interferon and ribavirin (PR) (Table S1).

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval by local Ethics Committees and informed consents were obtained.

Baseline-GRT was performed at clinician's discretion in 76/121 patients by Sanger-sequencing on NS3-protease (aa 1–181), NS5A domain I (aa 1-213) and/or NS5B (aa 1-591) genes, as elsewhere described (8-11). RASs were defined according to (3, 12, 13).

RESULTS

After a median (IQR) of 88 (49-120) weeks since PI-discontinuation, 14/58 patients tested still presented NS3-RASs able to confer cross-resistance to second-wave PIs (R155K, N=6;

R155T+D168N, N=1; Q80K, N=4; V170A±A156S, N=2; V36M+R155K, N=1). The prevalence of natural-RASs in NS5A and NS5B was of 11% (5/45 and 4/44, respectively). In addition, baseline-GRT followed by phylogenetic-analysis disclosed 4 cases (5.3%) of wrong GT-1b assignation by commercial assays (3 patients were infected by GT-1a, and 1 by GT-4d).

Patients started retreatment with median (IQR) baseline HCV-RNA of 5.9 (5.5-6.4) logIU/ml. One non-responder patient and 10 (8.3%) relapsers were observed, leading to a final SVR_{12} rate of 90.9% (110/121). SVR_{12} rates were 85.1% (40/47) in GT-1a patients, 80.0% (8/10) in patients with baseline-RASs, and 90.6% (58/64) in patients with baseline HCV-RNA>800,000 IU/ml. All non-cirrhotic patients achieved SVR_{12} *vs*. 89.5% of cirrhotic-patients (p=0.175, Table S2).

Fig.1 reports retreatment regimens in detail, along with the corresponding SVR_{12} rates.

According to the modality of retreatment choice, patients were divided into 3 groups.

The “GRT-guided“ group-A included 18 patients who either started a NS5A-containing recommended regimen (N=6), or a not-recommended PI-regimen (N=12) based on RASs profiles.

The “AASLD/EASL recommended, not GRT-guided” group-B included 72 patients who "switched" DAA-class, and received SOF+NS5A-inhibitor+RBV, with no prior NS5A-GRT.

Lastly, the “Not recommended, not GRT-guided” group-C included 31 patients, for whom nor GRT nor international guidelines were followed.

Even if only 18 patients were retreated with “GRT-guided” regimens, this approach let to an optimal efficacy (100% SVR_{12}), similar to “AASLD/EASL-recommended” regimens in group-B (94.4% SVR_{12}), and much greater than the 77.4% (24/31) SVR_{12} rate observed in group-C (p=0.011 by Fisher exact test; Table S2).

PIs were reused in 37 patients, and 33 (89.2%) reached SVR_{12}. All 10 patients treated with SOF+SIM after exclusion of NS3-RASs (group-A) achieved SVR_{12}, regardless RBV-administration

and treatment-duration. SVR_{12} was achieved also in the 7 patients receiving paritaprevir/ritonavir+ombitasvir+dasabuvir (3D)+RBV in groups A and C, regardless presence of baseline R155K NS3-RAS in one patient, confirming the efficacy of this regimens highlighted by previous real-life results (7).

PI-free, NS5A-based regimens were also highly effective. An *a posteriori* baseline-GRT performed in group-B, revealed 1 natural NS5A-RAS in 3 GT-1b patients (L28M-L31M-Y93H, respectively), and 2 NS5B-RASs (L159F+C316N) in another. Only the patient with L28M failed a recommended SOF+DCV+RBV regimen, while the other 2 reached SVR_{12} with a RBV-including, 24-week regimen.

The lowest SVR_{12} rates were observed in group-C among patients receiving SOF+RBV (3/6, 50%), or GT-1a patients receiving SOF+SIM±RBV without prior NS3-GRT (8/12, 66.7%). An *a posteriori* baseline-GRT performed in 3/4 of GT-1a SIM-failing patients revealed a pre-existing R155K NS3-RAS. Other 4 patients in group-C with baseline NS3-RASs (R155K=2; Q80K=1; A156S+V170A=1) treated for 24-weeks and/or with RBV reached SVR_{12}, plus a patient with Q80K receiving SOF+SIM for 12-weeks.

NS3- or NS5A-RASs were detected after retreatment in 4/7 virological-failures tested (Table 1).

SOF+RBV failing-patients showed no RASs emergence, even though one GT-1a had a natural L31M NS5A-RAS. Two group-B failing-patients had the double NS5A-RASs L28M+Y93H, and 2 were not tested for RASs.

Of the 4 GT-1a patients who failed SOF+SIM treatment, 2 showed Q80L+R155K or V36M+R155K RASs, 1 was not retested after failure, and 1 had never performed any NS3-GRT.

DISCUSSION

Baseline-GRT is widely used in retreatment settings in USA, thanks to the availability of commercial-assays, but until recent times Italy (as Europe) had poor access to it. Indeed, in our

study, even if some Italian centers offer internally-validated assays (8-11), in 69.5% of cases baseline-GRT was performed *a posteriori* for research purposes only, and not used to guide retreatment decisions. Nevertheless, GRT-guided regimens led to high SVR_{12} rates, even when they included a PI, whose reuse is not supported by current guidelines (1, 2).

Guidelines-recommended PI-free regimens were also highly effective. The combination of SOF+DCV+RBV led to 94.4% (17/18) SVR_{12}. Similarly, SVR_{12} rate was 95% (57/60) with SOF/LDV+RBV combination, concordant with the 96% SVR_{12} (74/77) from SIRIUS study in cirrhotic-patients (14), even if 59/60 of our patients were treated for 24 weeks instead of 12(14). Unfortunately, none of the 3 LDV-failing patients had performed a baseline NS5A-GRT to assess possible presence of natural NS5A-RASs.

A substantial proportion of patients (25.6%, 31/121) were retreated with a variety of "not-recommended, not GRT-guided" regimens, leading to the lowest SVR_{12} rates. This could be a consequence of the time-gap between the approval of first-generation PIs and full availability of NS5A-inhibitors, when retreatment choices for most urgent patients were limited to suboptimal regimens, such as SOF+RBV (50% SVR_{12} [3/6], supporting previous real-life data (5)), and SOF+SIM±RBV without prior NS3-GRT in GT-1a patients (66.7% SVR_{12}, 8/12).

Overall, even if firm conclusions cannot be drawn on the few patients we analyzed, our study encourage experienced laboratories, already present in several countries, to cooperate in offering clinicians reliable GRTs to personalize retreatments for PI-experienced patients, before considering not GRT-guided options. GRT can disclose possible misclassification of HCV-GT and can help retreatment choice accounting for RASs-presence. This approach would indeed limit as much as possible the chances of second-line failures and further development of multiresistant viruses, as well as high costs of third-line therapies.

FIGURE LEGENDS

Figure 1. SVR_{12} rates in patient subgroups. SVR_{12} rates obtained in protease-inhibitor experienced patients retreated with interferon-free regimens chosen according to GRT, EASL/AASLD recommendations, of none of them. Rates are reported separately for each drug-combination, ribavirin use and duration. The number of patients who relapsed, or presented resistance associated substitutions at baseline are shown. 3D, paritaprevir/ritonavir, ombitasvir and dasabuvir; AASLD, American Association for the Study of Liver Diseases; DCV, daclatasvir; EASL, European Association for the Study of the Liver; GRT, genotypic-resistance-test; IFN, interferon; LDV, ledipasvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR_{12}, sustained virological response; RAS, resistance associated substitution.

TRANSPARENCY DECLARATION

Dr. Ceccherini-Silberstein reports personal fees from Gilead Sciences, personal fees from Bristol-Myers Squibb, personal fees from Abbvie, personal fees from Roche Diagnostics, grants and personal fees from Merck Sharp & Dohme, personal fees from Janssen-Cilag, personal fees from Abbott Molecular, personal fees from ViiV Healthcare, outside the submitted work; and Valeria Cento reports personal fees from Abbvie, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen-Cilag. Carlo Federico Perno reports grants from Italian Ministry of Instruction, University and Research (MIUR), grants from Aviralia Foundation, during the conduct of the study; and personal fees from Gilead Sciences, Abbvie, Roche Diagnostics, Janssen-Cilag, Abbott Molecular, and grants and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, and ViiV Healthcare, outside the submitted work.

The other authors have nothing to declare.

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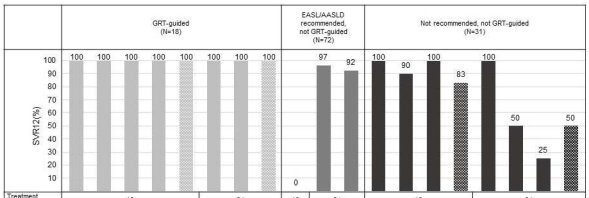
Table 1. Resistance associated substitution analysis in patients experiencing virological failure to second-line IFN-free regimens

ID	HCV genotype	HCV-RNA at baseline (IU/ml)	IFN-free treatment	Lenght (weeks)	Interval failure to retreatment (weeks)	At first PI failure	IFN-free treatment					
							At baseline			At relapse		
						NS3	NS3	NS5A	NS5B	NS3	NS5A	NS5B
AASLD/EASL recommended, not GRT-guided												
2286	1a	615458	SOF/LDV + RBV	24	157	V36M+ R155K	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
M01	1b	2,084,319	SOF/LDV + RBV	24	116	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2135	1b	442000	SOF/LDV + RBV	12	n.a.	V170A	V170A	n.a.	-	-	L28M+ Y93H	-
219	1b	10,471	SOF+DCV + RBV	24	119	-	-	L28M	-	-	L28M+ Y93H	-
Not recommended, not GRT-guided												
330	1a	9,234,587	SOF+SIM + RBV	12	117	R155K	-	-	-	Q80L+ R155K	-	-
172	1a	116,116	SOF+SIM + RBV	24	78	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PAO-2	1a	3,286,645	SOF+SIM	24	68	V36M+ R155K	R155K	-	-	V36M+ R155K	-	-
2323	1a	1393000	SOF+SIM	12	133	R155K	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
211	1a	1,104,189	SOF+RBV	24	80	R155K	R155K	-	-	-	-	-
281	1b	157,383	SOF+RBV	24	39	T54S	T54S	-	-	-	-	-
558	1a	2,731,632	SOF+RBV	24	120	-	-	L31M	-	n.a.	L31M	-

AASLD, American Association for the Study of Liver Diseases; DCV, daclatasvir; EASL, European Association for the Study of the Liver; GRT, Genotype resistance testing; INF, interferon; IU, International unit; LDV, ledipasvir; n.a., not available; PI, protease-inhibitor; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.



Treatment duration (weeks)	12					24			12	24		12				24				
Ribavirin	Ribavirin				No ribavirin	Ribavirin		No ribavirin	Ribavirin	Ribavirin		Ribavirin			No ribavirin	Ribavirin				No ribavirin
IFN-free regimen	SOF/ LDV	SOF+ DCV	3D	SOF+ SIM	SOF+ SIM	SOF+ DCV	SOF+ SIM	SOF+ DCV	SOF/ LDV	SOF/ LDV	SOF+ DCV	3D	SOF+ SIM	SOF	SOF+ SIM	3D	SOF+ SIM	SOF	SOF+ SIM
SVR_{12}, n/N (%)	1/1 (100)	1/1 (100)	2/2 (100)	5/5 (100)	2/2 (100)	3/3 (100)	3/3 (100)	1/1 (100)	0/1 (0)	56/58 (97)	12/13 (92)	3/3 (100)	9/10 (90)	2/2 (100)	5/6 (83)	2/2 (100)	1/2 (50)	1/4 (25)	1/2 (50)
Virological failure, N	0	0	0	0	0	0	0	0	1	2	1	0	1	0	1	0	1	3	1
RASs prevalence, n/N (%)	0/1 (0)	0/1 (0)	0/2 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/3 (0)	-	-	2/9 (22)	2/5 (40)	0/1 (0)	2/7 (29)	0/2 (0)	1/3 (33)	1/2 (50)	1/1(100)	0/4 (0)	1/1 (100)