Clinical characterization and economic impact evaluation of anti-HCV DAA treatment failure: real life data from theItalian Platform for the Study of Viral Hepatitis Therapies (PITER)

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BACKGROUND

•The dichotomy of HCV is that the overall number of infections is projected to decline, the number of individuals experiencing advanced liver disease, liver related deaths and healthcare costs are expected to increase. DAAs have been reported to have extremely high efficacy. For HCV therapy to be considered successful, its use should result in viral clearance with a sustained virologic response (SVR), as well as improved clinical outcomes. However, this success depends on the severity of liver disease. Moreover, although rare, the failure to eradicate HCV RNA with DAAs remains an important challenging.

AIM

•To evaluate the prevalence of treatment failure and its correlates (i.e., disease severity and specific DAA regimen) in a large real-life sample of patients, specifically, those included in the PITER Cohort Study (Italian Platform for the Study of Therapies for Viral Hepatitis). The clinical and economic burden of treatment failure, according to the severity of liver disease, were also estimated

METHODS

The study was conducted among patients attending 23 clinical centers involved in PITER. The study population consisted of consecutive patients for whom the 12-week post-treatment HCV RNA evaluation was performed from January 2015 to May 2016. Data were collected on the DAA regimen used, the HCV genotype, and the liver fibrosis stage. Detailed clinical data from patients who failed to reach SVR following the first DAA regimen and data on retreatment, were evaluated. Resource consumption was prospectively determined for each patient based on the clinical notes from the outpatient visit or hospital admission following the failure event

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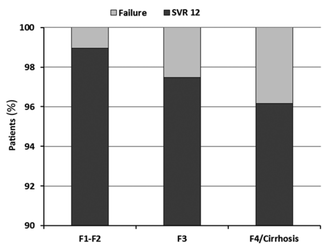
RESULTS

From January 2015 to June 2016, 3,926 patients consecutively underwent IFN-free DAA treatment and reached the 12-week post-treatment evaluation. Their median age was 60 years (range: 34-84 years) and 2,594 (66.1%) were male. Of these patients, 140 (3.6%) failed to achieve SVR [median age: 57 years (range: 34-80 years); 108 (77.1%) males; 59 (42.1%) IFN-experienced]. Among the 140 patients who did not achieve SVR, 4 (2.9%) were non-responders, and 3 (2.1%) were considered as breakthrough at the 8th week and 12th week of treatment. The remaining 133 patients (95%) had achieved HCV-RNA clearance at the end of treatment, and relapsed thereafter. **The DAA regimens used overall and in patients who experienced treatment failure, according to HCV genotype, are reported in Table 1**

	Overall	HCV genotype Number of Failures/Number of Patients treated (%)						
DAA regimen	Number of Failures/Number of Patients treated (%)	1	1a	1b	2	3	4	5
	140/3926 (3.6%)							
SOF+RBV	69/747 9.2%	4/5 80%	4/13 30.7%	18/53 33.9%	8/536 1.5%	32/132 24.2%	3/8 37.5%	-
SOF+SIM ±RBV	38/713 5.3%	1/5 20%	7/94 7.4%	24/549 4.4%	½ 50%	1/1 100%	3/61 4.9%	1/1 100%
SOF+LDV±RBV	16/1031 1.6%	0/16 0%	3/199 1.5%	10/766 1.3%	-	0/1 0%	3/44 6.8%	0/5 0%
3D±RBV	9/894 1%	0/3 0	3/57 5.3%	6/689 0.9%	0/143 0%	-	0/2 0	-
2D+RBV	2/64 3.1%	-	-	-	-	-	2/59 3.4%	0/5 0%
SOF+DCV±RBV	6/471 1.3%	0/7 0	0/45 0	1/110 0.9%	0/55 0	5/244 2%	0/10 0%	
SIM+DACL	0/6 0%	-	-	0/6 0%	-	-	-	-

The failure rate, by baseline fibrosis stage, is reported in Figure 1.



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Post-failure clinical and consume resource data

The median follow-up time following the end of the first DAA regimen in the 140 patients who failed to achieve SVR, was 6.4 months (range: 1.2-17.9 months).

Following failure:

HCC was diagnosed at the end of treatment in 6 (5%) patients and during a median follow up of 6 months in 10 (8.3%) patients .In 7 (5.8%) patients, the diagnosis was a HCC recurrence.

Five patients with liver cirrhosis underwent OLT .The Child-Pugh class changed from A to B in 15 (12.4%) patients and from B to C in 1 (0.8%) patient. In patients with an increase in the Child-Pugh class, the median MELD score was 9 (range: 7-13) at baseline and 12 (range: 9-15) following treatment failure ($p<0.05$). In patients in whom the Child-Pugh class did not change after failure ,MELD score was similar in both Child-Pugh class A and class B patients.

Ascites appeared in 15 of the 121 patients with cirrhosis (12.4%); in 3 (20.%) of the 15 patients, it constituted the first decompensation. Nine (7.4%) patients manifested hepatic encephalopathy; in 3 (33.3%) of them, it appeared for the first time following treatment failure.

Forty patients (28.5%) were hospitalized (33 as ordinary admissions and 7 in day hospitals). Among hospitalized patients, the number of diagnostic procedures was the cost driver with the second highest costs, following hospital admission. The overall mean cost for each patient (excluding costs for DDA and concomitant drugs) was €18,606.557patient. For patients who were not hospitalized, the cost of laboratory tests was the highest cost driver; mean overall cost of €693.54/patient.

CONCLUSIONS

Although treatment failure is uncommon, its clinical and economic consequences are important.

Because some of the DAA regimens evaluated have since been deemed suboptimal,

the use of appropriate DAA regimens is expected to reduce the failure rate. However, "curing" HCV requires more than achieving SVR; Lt is necessary to treat not only select patients with more severe liver disease but also patients with earlier disease stages, which could reduce the failure rate, increase the clinical benefits of treatment, and decrease the costs of disease management.

The estimated direct costs following treatment failure, by age class and stage of liver disease, are reported in Table 2.

Age Class (in Years)	F3 Fibrosis N. patients	Direct Costs (€)/patients	F4 Fibrosis N. patients	Direct Costs (€)/patients	Liver failure N. patients	Direct Costs (€)/patients	HCC N. patients	Direct Costs (€)/patients	OLT N. patients	Direct Costs (€)/patients
34-50	4	€ 1.666,58	26	€ 675,39	1	€ 98,13	3	€ 31.192,94	2	€ 62.876,68
51-60	4	€ 210,63	33	€ 562,38	5	€ 2.473,04	8	€ 14.800,44	3	€ 63.640,90
61-70	4	€ 1.145,14	18	€ 516,22	2	€ 5.880,80	2	€ 8.947,61	0	€ 0,00
71-80	5	€ 783,33	7	€ 584,83	4	€ 6.945,24	8	€ 9.586,50	0	€ 0,00

	Patients who received a second DAA treatment, by type of first regimen and HCV genotype (n=72 patients)									
	Second DAA Regimen									
First DAA Regimen	SOF+DCV Number of patients (%)					SOF+LDV Number of patients (%)				Other Regimens
	N. patients 38 (52.7%)	Gt1	Gt2	Gt3	Gt4	N patients 27 (37.5%)	Gt1	Gt3	Gt4	N patients 7 (9.7%)	Gt1,Gt3,Gt4
SOF+RBV	29	7 (24.1)	3 (10.3)	19 (65.5)		14	11 (78.6)	1 (7.1)	2 (14.2)	1	PEG+SOF+RBV (Gt3)
SOF+SMV	9	7 (77.8)	-	-	2 (22.2)	13	13 (100)			2	3D (Gt1); 2D (Gt4)
SOF+LDV	-	-	-	-	-	-	-	-	-	4	3D; (Gt 1) SOF+SIM (Gt1 and Gt4)