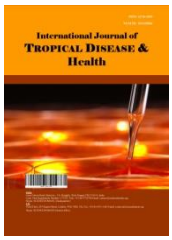

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Management of Hepatitis C Virus Genotype 4 Treatment Failure: A Real-World Single Center Experience

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Treatment failure with direct-acting antiviral (DAA) therapy is associated with worsening of liver disease especially in cirrhotic patients. Moreover, data on retreatment of HCV genotype 4 patients (G4) with DAA failure are still very limited, since they are under- represented in most clinical trials.
Aims: To evaluate the efficacy of retreatment of Egyptian HCV G4 DAA failure patients based on the use of a new DAA class from currently available first- generation DAA regimens other than the patient had relapsed to.
Methods: 29 *E*gyptian HCV G4 DAA failure patients were retreated by switch to a new DAA class from first- generation DAA regimens than the patient had relapsed to independent of RAS testing. 25 out of these 29 patients completed retreatment and 4 patients were lost for follow–up.
Results: Among other risk factors, by logistic regression analysis, only older age, high CTP score and high base-line viral load were independent predictors of DAA failure among our cohort. Also SOF/RBV regimen was the most common prior DAA regimen associated with treatment failure (48.3%).
All our DAA failure patients were cirrhotics that made prompt retreatment of them a rescue strategy to halt viral replication and disease progression.

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After retreatment, 22 (88%) of the 25 patients who completed retreatment achieved SVR12 and the remaining 3 (12%) failed.
These 3 patients completed a second retreatment, one achieved SVR and the other 2 relapsed again (re-relapsers)
Conclusion: The overall SVR rate (88%) demonstrated in this real –world study, clearly shows that, the retreatment policy of DAA failure patients by switch to – or addition of a new drug class independent of RAS testing is a good retreatment option, that may be of importance for many areas of the world with no or difficult access to RAS testing or second-generation rescue regimens.

Keywords: Treatment failure; direct acting antiviral therapy (DAAs); retreatment; HCV genotype 4 (G4).

1. INTRODUCTION

According to recent estimates, hepatitis C virus (HCV) infection affects approximately illion people or 1% of the entire world population [1]. Moreover, chronic HCV infection is associated with substantial morbidity and mortality, with liver-related complications including cirrhosis, liver failure and hepatocellular carcinoma (HCC) [2].

The goal of antiviral therapy is to prevent these complications by achieving viral eradication which is defined as undetectable HCV RNA 12 weeks after the end of treatment also called sustained virologic response (SVR) [2].

The recent introduction of direct–acting antivirals (DAAs) has revolutionized HCV therapy with SVR rates exceeding 90% irrespective of liver disease severity or history of previous therapy [3]. These drugs target the 3 HCV enzymatic nonstructural proteins including NS3/4A protease inhibitors (telaprevir, boceprevir, simeprevir, paritaprevir), NS5A replication complex inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir) and NS5B polymerase inhibitors, such as the nucleos(t)ide analogue (sofosbuvir) and non-nucleoside analogue (dasabuvir) [4].

Despite the excellent efficacy of all-oral DAA combination therapy, treatment failure still occurs among different patient populations, for which decision about ***retreatment*** regimen remains an important challenge [3].

Treatment failures are usually related to relapse and less often to on-treatment virus breakthrough [5]. The reason for treatment failure isn't yet clearly elucidated, but several viral and host factors can exist which include the emergence of HCV resistant associated substitutions (RASs), HCV genotype, viral load, the presence of cirrhosis, comorbidities and adherence to treatment [6].

RASs which reduce susceptibility to DAA agents, are commonly but not always, observed after DAAs failure, and especially NS5A RASs that usually persist for years, may impact ***retreatment*** options [7]. Nonetheless, viral relapse can still occur in absence of detectable RASs and even with the use of highly effective DAAs, so that the true impact of RASs in therapeutic failure remains to be determined [4].

Considering the presence of advanced fibrosis in most patients with treatment failure, prompt ***retreatment*** to halt viral replication and disease progression would be more than desirable.

So far, there are 8 major HCV genotypes, and genotype 4 (GT4) represents more than 90% of all HCV cases in Egypt, while the remaining 10% is due to HCV genotype 1 [2].

Generally, there are limited data on the outcomes of ***retreatment*** of HCV patients after DAA failure in real-world setting [3]. Moreover, data on ***retreatment*** of HCV G4 patients with DAA failure are still very limited, since G4 patients with DAA failure under-represented in most clinical trials [2]. Consequently, ***retreatment*** of this group of patients remains somewhat speculative and represents a significant challenge.

Recently, two pangenotypic DAA drug combinations GLE/PIB and SOF/VEL/VOX have been approved by both EASL and AASLD for salvage therapy of DAA failure. However, both are not available or marketed in many resource – limited countries including Egypt during the study period [7].

Considering this and the lack of cross–resistance among different DAA classes, one reasonable approach for ***retreatment*** after DAA failure in the presence of RASs is to switch DAA class [8].

2. PATIENTS AND METHODS

In the period from September 2018 to February 2019 a total of 29 Egyptian patients with HCV G4 infection who failed to respond to previous DAAs therapy were selected and identified from Tanta Liver Center (TLC).

2.1 Inclusion Criteria

All HCV G4 patients who failed previous treatment with DAA therapy were included in the study after informed or written consent.

2.2 Exclusion Criteria

- Patients with HCV/HBV co-infection.
- Patients with HCV/HIV co-infection.
- Overt hepatic encephalopathy.
- Patients with HCC before ablation therapy.

2.3 All the Study Groups were Subjected to the Following

1) Full history taking including previous DAAs therapy and its duration.
2) Complete physical examination searching for stigmata of liver disease.
3) Laboratory studies including: urine, CBC, random blood sugar, prothrombine (activity & INR), liver biochemical tests (bilirubin, ALT, AST, Serum albumin) and HCV RNA by RT PCR.
4) Abdominal US scan.
5) The severity of liver disease was determined by CTP score depending on clinical, biochemical and ultrasonographic findings.
6) Retreatment regimen: All the study group were retreated with another DAAs combination containing in most cases sofosbuvir (due to its high barrier to resistance) with a different DAAs class than the patient had relapsed to. The choices of drugs were restricted to currently available first-generation DAA regimens at certain time points during the study period from September 2018 to February 2019.

Due to financial and technical difficulties, no resistance testing was performed before retreatment. Also the 2 recently approved potent pangenotypic second –generation DAA rescue regimens (GLE /PIB&SOF/VEL /VOX) were not available or marketed yet in Egypt during the study period. The choice of drugs and the use of ribavirin were at the discretion of the treating physician and the availability of drugs at certain time points in Egypt.

7) The response to therapy was monitored by follow-up laboratory studies performed 4w and 12w after initiation of therapy as well as 12w after the end of treatment including HCV RNA by RT PCR.
8) Any treatment-related adverse events were recorded and dealt with accordingly.

3. RESULTS AND DISCUSSION

A total of 29 Egyptian CHC G4 patients who failed to respond to previous DAAs therapy were the subject of the present study. They were selected and identified from 431 CHC G4 patients treated with DAAs therapy at Tanta Liver Center (TLC).402(93.3%) out of these 431 patients achieved SVR and the remaining 29(6.7%) patients who were the subject of the present analysis failed. Therefore, the rate of treatment failure among our cohort with DAAs therapy is 6.7%.

The base-line characteristics of our study group with first-line DAA failure are reported in table (1).Astatically significant difference was observed when patients with treatment failure were compared to those who achieved SVR in terms of age, male sex, presence of cirrhosis, CTP score, base-line viral load and comorbidities (Tables 2, 5).

Therefore, all the 29 patients with DAA failure in the study were cirrhotics, predominantly males, of relatively older age, with more frequent comorbidities and high base-line viral load. However according to logistic regression analysis, only older age, high initial CTP score and high base-line viral load are independent predictors of treatment failure (Table7).

Additionally, about 50%of the DAA failure patients had been previously treated with SOF /RBV regimen (Table 6). Therefore, SOF/RBV is the most common first – line DAA regimen associated with treatment failure.

Also, 5 out of 29 retreated patients had well ablated HCC, 4 of them completed retreatment and one patient was lost for follow- up.

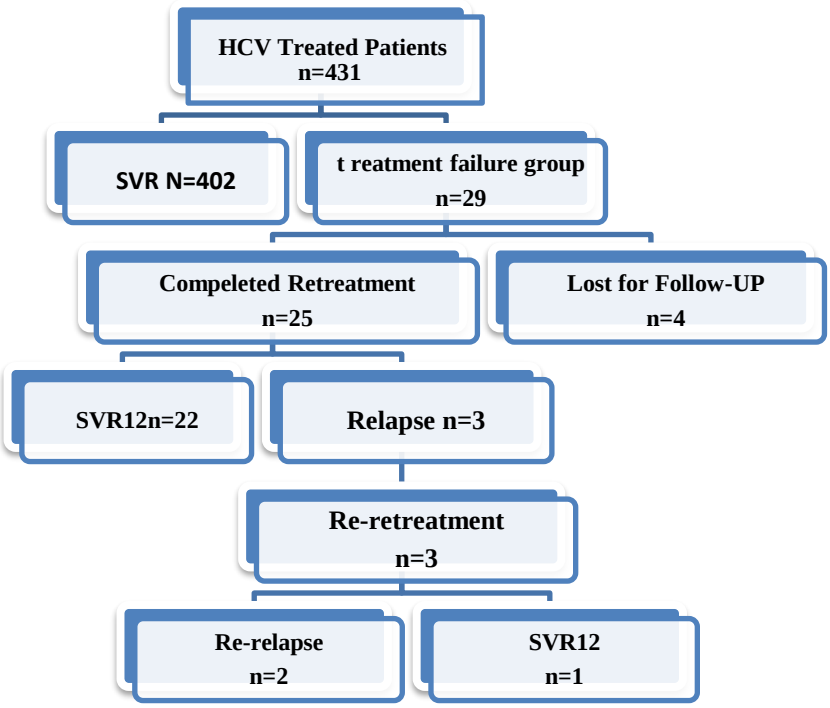

Fig. 1. Flow chart of our HCV treated patient

3.1 Outcome of Retreatment

25(86.2%) out of our 29 retreated patients completed retreatment and 4(13.8%) were lost for follow-up.

Out of the 25 patients who completed retreatment 22(88%) achieved SVR12 and the remaining 3(12%) patients failed.

Therefore, the overall SVR rate achieved in the DAA failure patients after retreatment was 88% (Tables 8, 9, 10, 11, 12).

The 3 patients (12%) who failed retreatment were all (100%) males, diabetic with advanced cirrhosis (mean CTP =9.33) and 2 of them were retreated by mistake with another drug from the same class they had relapsed to (NS5A inhibitors). These 3 re-relapsers completed a second retreatment, one (33.3%) of them achieved SVR12 (CTP=7) and the other 2(66.7) relapsed again. Both had had decompensated cirrhosis with CTP score of 10 &11 respectively.

Regarding the outcome of retreatment of the 5 patients with ablated HCC who failed previous DAA therapy. 3 (75%) out of the 4 HCC patients who completed retreatment achieved SVR and the remaining patient (25%) failed. Therefore, the SVR rate of this subpopulation was lower (75%) than the overall SVR rate of whole study population (88%) (Table 13).

3.2 Discussion

The overall failure rate of DAA therapy in this real- world study was 6.7% (29 out of 431). Review of relevant publications revealed a relatively lower DAA failure rate reported by the other real –world studies (5.3%, 5%, 3.6% and 3.1%) [6,9-11]. These discrepancies may be related to heterogeneity of the populations included in all these studies, in terms of patient's characteristics, genotypes and DAA regimens used.

Analysis of ***demographic and clinical characteristics of the study group*** with DAA failure revealed that, older age, male sex, presence of cirrhosis, high base-line viral load and comorbidities were significantly represented among the patients with DAA failure compared to those of the SVR group (Tables 2, 5). Consequently, this provides evidence that these shared features or *risk factors* may have contributed to treatment failure among the DAA treated patients. By logistic regression analysis, only older age, CTP score and base-line viral load are independent predictors of treatment failure.

Table 1. Demographic data of the treatment failure group (n=29)

	No.	%
AGE (YEARS)		
MIN. – MAX.	34.0 – 74.0	
MEAN ± SD.	55.21 ± 8.47	
MEDIAN	55.0	
SEX		
MALE	25	86.2
FEMALE	4	13.8
RESIDENCE		
RURAL	24	82.8
URBAN	5	17.2
CIRRHOSIS	29	100.0
COMPENSATED	(24)	(82.8)
DECOMPENSATED	(5)	(17.2)
CTP SCORE		
CHILD A	16	55.2
CHILD B	8	27.6
CHILD C	5	17.2
COMORBIDITIES	18	62.1
DM	13	44.8
THYROID	2	6.9
CKD	1	3.4
AIH	1	3.4
LYMPHOMA	1	3.4
PREVIOUS IFN THERAPY	5	17.2
LEVEL OF VIREMIA IU/ML		
MIN. – MAX.	3196 – 3374747	
MEAN ± SD.	811577.7 ± 1169617	
MEDIAN	214446	

Table 2. Demographic characteristics of the treatment failure group compared to those of the SVR group

VARIABLE	Treatment failure group (n=29)		SVR group (n=402)		Test of Sig.	p
	No.	%	No.	%		
SEX						
MALE	25	86.2	208	51.7	χ^2= 8.056*	0.005*
FEMALE	4	13.8	194	48.3		
AGE (YEARS)						
MIN. – MAX.	34.0 – 74.0		33.0 – 55.0		t=4.288*	<0.001*
MEAN ± SD.	55.21 ± 8.47		47.0 ± 5.88			
MEDIAN	55.0		47.0			
RESIDENCE						
RURAL	24	82.8	305	75.9	χ^2=	0.517
URBAN	5	17.2	97	24.1	0.420	
COMORBIDITIES						
NO	11	37.9	277	69.0	χ^2=	0.018*
YES	18	62.1	125	31.0	5.613*	
CIRRHOSIS						
NO	0	0	115	28.6	χ^2=	0.001*
YES	29	100	287	71.4	11.315*	

Table 3. US findings of the treatment failure group (n=29)

US Findings	No.	%
LIVER STATUS		
SIZE		
NORMAL	10	34.5
ENLARGED	10	34.5
SHRUNKEN	9	31.0
ECHO PATTERN		
CIRRHOTIC	21	72.4
BRIGHT	4	13.8
MIXED PPF & CIRRHOSIS	4	13.8
HEPATIC FOCAL LESION	5	17.2
SPLEEN		
ENLARGED	24	82.8
NORMAL	4	13.8
SPLENECTOMY	1	3.4
ASCITES	**5**	**17.2**
MILD	4	80.0
MARKED	1	20.0

Similar results were also reported by other relevant real –world studies but with few discrepancies [12,13].

By contrast, a very recent multicenter study conducted by Dietz et al (2021) found no statistically significant difference between SVR and failure patients regarding the presence of cirrhosis and other clinical parameters [7].

Although, treatment failure is uncommon, its clinical consequences are important particularly in cirrhotic patients. In this subset of patients, treatment failure was associated with worsening liver disease, decompensation and liver related deaths due to continuous viral replication and necro-inflammatory activity [8].

Considering that all the DAA failure patients had liver cirrhosis and about 50% of them had advanced liver disease (Child´s class B or C), prompt retreatment was considered a rescue strategy to halt viral replication and disease progression [14].

With regard to the retreatment of the patients after a first –generation DAA treatment failure, the very potent, single tablet, pangenotypic second-generation DAAs, recently approved as a salvage therapy for DAA failure were not available or marketed yet in Egypt at the time of retreatment decision (SOF/VEL/VOX&GL/PIB).

Considering this and the lack of cross –resistance among different DAA classes, one reasonable approach for retreatment after DAA failure in presence of RASs is to **switch DAA class** [8].

Based on the above mentioned data together with the difficult access to RAS testing in the center, we retreated the cohort with DAA failure using sofosbuvir in combination with a new first-generation DAA class (**switch from class to another**) independent of RAS testing.

Regarding the outcome of retreatment, 22(88%) of 25 patients who completed retreatment achieved SVR12 and only 3(12%) patients failed.

The overall high SVR rate (88%) reported in the study supported by other real-world studies indicate that the concept of HCV retreatment by switch to- or addition of anew DAA class independent of RAS testing is a feasible and successful strategy, which may be of importance for many area of the world that have no or difficult access to RAS testing or second-generation DAA rescue regimens like our country.

In this regard, similar results were reported by the few relevant real world studies (85% Dietz et al. [7] & Piecha et al. [15]. and 86% by Zarębska-Michaluk et al. [3]. Meanwhile, kondili et al. [11] reported 94.8% SVR rate on retreatment of 72 cirrhotic patients with first-generation DAAs lasting 24 weeks.

Table 4. Initial laboratory findings in the treatment failure group compared to those of SVR group

VARIABLE	TREATMENT FAILURE GROUP (N=29)	SVR GROUP (N=402)	T	P
HB				
MIN. – MAX.	10.50 – 16.70	11.50 – 17.20	3.251*	0.002*
MEAN ± SD.	12.82 ± 1.68	14.14 ± 1.41		
MEDIAN	12.40	14.30		
PLATELETS				
MIN. – MAX.	44.0 – 360.0	54.0 – 418000	14.724*	<0.001*
MEAN ± SD.	115.14 ± 68.57	156205.1 ± 57027		
MEDIAN	91.0	154000		
WBCS				
MIN. – MAX.	2100.0 – 8300.0	2100.0 – 13500.0	2.388*	0.017*
MEAN ± SD.	4895.86 ± 1834.86	6547.5± 3688.4		
MEDIAN	4800.0	6000.0		
BILIRUBIN				
MIN. – MAX.	0.30 – 3.90	0.32 – 3.86	1.456	0.151
MEAN ± SD.	1.49 ± 0.90	1.17 ± 0.76		
MEDIAN	1.40	1.0		
INR				
MIN. – MAX.	1.08 – 1.90	1.0 – 1.90	2.860*	0.006*
MEAN ± SD.	1.36 ± 0.27	1.18 ± 0.22		
MEDIAN	1.30	1.12		
ALT				
MIN. – MAX.	10.80 – 140.0	10.0 – 59.0	2.499*	0.017*
MEAN ± SD.	52.20 ± 31.07	36.72 ± 12.12		
MEDIAN	41.0	38.0		
AST				
MIN. – MAX.	15.0 – 122.0	17.0 – 57.0	3.170	0.003*
MEAN ± SD.	51.55 ± 25.27	35.38 ± 10.78		
MEDIAN	45.0	33.0		
S ALBUMIN				
MIN. – MAX.	2.40 – 4.30	3.40 – 4.90	7.728*	<0.001*
MEAN ± SD.	3.41 ± 0.51	4.29 ± 0.35		
MEDIAN	3.50	4.30		

Table 5. Initial CTP score and viral load of the treatment failure group compared to that of the SVR group

	TREATMENT FAILURE GROUP	SVR GROUP	t	p
CTP	**(n=29)**	**(n=402)**		
MIN. – MAX.	5.0 – 11.0	5.0 – 8.0	4.276*	<0.001*
MEAN ± SD.	6.97 ± 1.99	5.28 ± 0.75		
MEDIAN	6.0	5.0		
VIRAL LOAD	(n=29)	(n=29)		
MIN. – MAX.	3196 – 3374747	4146.0 – 764161	2.500*	0.015*
MEAN ± SD.	811577.69±1169616.5	257920.14±232401.79		
MEDIAN	214446.0	153146.0		

Table 6. Prior DAAs therapy before retreatment (n=29)

Regimen	No.	%
SOF/RBV	14	48.3
SOF-DCV ± RBV	5	17.2
IFN-SOF ± RBV	4	13.8
SIM-SOF± RBV	3	10.3
SOF-LDV ± RBV	3	10.3

Table 7. Univariate and multivariate Logistic regression analysis for the parameters affecting failure group (29/402)

	Univariate		#Multivariate	
	P	**OR (95%C.I)**	**P**	**OR (95%C.I)**
SEX (MALE)	0.001*	0.172 (0.059 – 0.502)	0.174	0.347 (0.076 – 1.595)
AGE (YEARS)	<0.001*	0.765 (0.685 – 0.853)	<0.001*	0.712 (0.615 – 0.825)
COMORBIDITIES	0.001*	0.276 (0.127 – 0.601)	0.090	0.313 (0.082 – 1.199)
CIRHOSIS	0.996	–		
HB	0.004*	1.436 (1.125 – 1.833)	0.777	1.072 (0.663 – 1.734)
PLATELETS	0.001*	3.321 (1.592 – 6.929)	0.996	0.997 (0.301 – 3.308)
WBCS ($\times 10^3$)	<0.001*	1.574 (1.248 – 1.984)	0.377	1.206 (0.796 – 1.829)
BILIRUBIN	0.007*	0.586 (0.397 – 0.866)	0.544	0.743 (0.284 – 1.940)
INR	0.001*	0.102 (0.027 – 0.388)	0.378	3.504 (0.216 – 56.877)
ALT	0.561	1.003 (0.993 – 1.013)		
AST	0.309	1.006 (0.995 – 1.017)		
S ALBUMIN	<0.001*	5.988 (2.971 – 12.068)	0.420	1.973 (0.378 – 10.291)
CTP	<0.001*	0.373 (0.272 – 0.512)	<0.001*	0.172 (0.083 – 0.355)
VIRAL LOAD ($\times 10^6$)	<0.001*	0.227(0.111 – 0.468)	<0.001*	0.085 (0.023 – 0.319)

Table 8. Outcome of retreatment of SOF/RBV treated group (n=13)

Retreatment regimen	Outcome	
	SVR 12	**Treatment failure**
SIM/SOF/±RBV	No.=5	-
N=5	100%	
SOF/LDV/±RBV	No.=4	-
N=4	100%	
SOF/DCV/±RBV	No.=4	-
N=4	100%	
Total	13	-
	100%	

Table 9. Outcome of retreatment of IFN/SOF/RBV treated group (n= 4)

Retreatment Regimen	Outcome	
	SVR 12	**Treatment failure**
SOF-DCV-RBV	No.= 3	-
N=3	100%	
SIM-SOF	No.= 1	-
N= 1	100%	
Total	4	-
	100%	

Indeed, simple comparison of SVR rates in this study and the other real-world studies seems to be difficult and unreliable due to heterogeneity of populations included in all these studies, in terms of patient's characteristics, severity of liver disease, sample size, genotype as well as antiviral regimens and its duration.

Table 10. Outcome of retreatment of SOF/DCV/±RBV treated group (n= 4)

RETREATMENT REGIMEN	OUTCOME	
	SVR12	Treatment Failure
SIM/SOF/ RBV N=2	No.= 2 100%	-
SOF/3D/RBV N= 1	No.= 1 100%	-
SOF/LDV/RBV N= 1	-	No.= 1 100%
Total	4 100%	-

Table 11. Outcome of retreatment of SOF/ LDV/± RBV treated group (n= 2)

Retreatment Regimen	Outcome	
	SVR 12	Treatment Failure
SOF/ DCV/ RBV N= 1	-	1 100%
SOF/ 3D/ RBV N= 1	No.=1 100%	-
Total	1 50%	1 50%

Table 12. Outcome of retreatment of SIM/ SOF/ ±RBV treated group (n= 2)

Retreatment Regimen	Outcome	
	SVR 12	Treatment Failure
SOF/ DCV/ RBV N= 1	1 100%	-
SOF/ LDV/RBV N= 1	-	1 100
Total	1 50%	1 50%

Table 13. Outcome of retreatment of HCC patients who completed retreatment n=4

	SVR 12	Treatment Failure
SIM/SOF/RBV **N= 3**	3 100%	-
SOF/LDV/RBV **N= 1**	-	1 100%
Total	3 75%	1 25%

It is noteworthy to mention that, lack of RAS testing before initiation of retreatment did not seem to affect retreatment results in this study (88% SVR rate), an observation that has also been reported by other real-world studies [15].

On the other hand, the 3 patients (12%) who failed retreatment in this study were all (100%) males, diabetic with advanced cirrhosis (mean CTP=9.33),.and 2 of them were retreated by mistake with another drug from the same DAA class they had relapsed to (NS5A inhibitors).. Once again, adding more support to the validation of the concept of HCV retreatment by switching to-or addition of a different DAA class. Moreover, similar results were also reported by the real-world study of Dietz et al. [7].

The 3 patients who failed retreatment completed a second retreatment, one of them achieved SVR12 and the other 2 relapsed again. These 2 re-relapsers had decompensated cirrhosis with a

CTP score of 10&11 respectively that might be behind their multiple treatment failure.

Currently, there is no data to guide retreatment of patients who failed more than two DAA treatment courses; therefore an individualized treatment concept is warranted in these patients.

Strikingly, 3(75%) of 4 patients with successfully ablated HCC who completed retreatment achieved SVR12 and the remaining one (25%) failed, indicating that the SVR in this subpopulation is lower than the overall SVR of the whole study population (88%). Moreover, no HCC recurrence was observed in the 3 HCC patients who achieved SVR during 6 months of extended follow-up and this positive impact has been reported in other international studies [16,17]. Consequently, DAA therapy should not be withheld in this subpopulation.

Despite high SVR rate (88%) demonstrated in the present study by retreatment of HCVG4 patients who failed previous DAA therapy, this study had some limitations. The major limitation was the relatively small number of patients included being a single center experience. Another limitation was lack of RAS testing before retreatment due to difficult access to testing as well as financial reasons. Also it was difficult to provide more information on the retreatment results in patient who previously failed two or more DAA courses due to the small number of patients within the cohort (3 patients).

The strengths of the present study include its timeliness, real-world setting that allowed the report on the experience in the retreatment concept of DAA failure patients by switch to or addition of a new drug class.

4. CONCLUSION AND RECOMMENDA-TIONS

Based on the results of the present study, **the retreatment policy by a switch to or addition of a new drug class is a good retreatment option,** that may be of importance for many areas of the world with no or little access to RAS testing or second-generation DAA rescue regimens.

To the best of our knowledge, this study may be the first of its kind to retreat HCV G4 patients with DAAs failure by this concept in Egypt.

The risk factors for DAA failure in our study group were the presence of cirrhosis, male gender, older age, high base-line viral load and associated comorbid disease particularly diabetes mellitus, however by logistic regression analysis, only older age, high CTP score and high base-line viral load are independent predictors of DAA failure.

Based on the results of this real- world study we suggest that all HCVG4patients with DAA failure should be considered for retreatment to halt viral replication and consequently progression of liver disease, thus providing a new hope for this group of critically ill patients in Egypt.

Needless to say that, it is necessary to consider not only efficacy, but also cost in selection of anti- HCV therapy particularly in resource - limited countries.

The experience reported in the present study with overall SVR rate of 88% confirms the retreatment policy by switch to- or addition of a new drug class independent of RAS testing is a good retreatment option that may be of value for many resource- limited countries with no or difficult access to RAS testing or second generation DAA rescue therapy.

Our study may be the first of its kind to initiate therapy of HCV G4 patients with DAA failure by the policy of switch to- or addition of a new drug class independent of RAS testing in Egypt.

Although, the real world quality, the single center design, standardized monitoring procedures and high overall SVR rate (88%) represent strengths of this study, limitations need to be considered.

The relatively small sample size is one of these limitations, therefore a large scale multicenter study covering all geographical areas in Egypt is recommended to verify or confirm these results.

Interestingly, lack of RAS testing before retreatment that could be considered by some another limitation did not seem to affect the results of retreatment in our study (SVR rate =88%), therefore, RAS testing is only recommended in selected populations.

Also due to small number of patients (3 only) we weren't able to provide a more information about the results of retreatment of patients with multiple (2 or more) DAA treatment failure, an issue that hasn't been properly assessed in the literature, therefore we recommend larger studies in this regard.

Finally, this modest effort in the sitting of limited resources does provide hope as well as expert insight regarding retreatment of our Egyptian HCVG4 cirrhotic patients with DAA failure that should be useful to practicing physicians and health authorities in the field of hepatogastroentrology.

CONSENT

An informed consent was taken from each patient which includes:

a) Aim of the research.
b) All data are confidential.
c) All data was used in the research only.

Participants privacy:

a) The names of participants were hidden.
b) There was code number for each participant in a special folder.
c) The result of the research was used in scientific publishing only.

ETHICAL APPROVAL

This study was approved by the local ethical committee of Tanta Faculty of Medicine.

Any unexpected adverse events appeared during the course of the research was cleared to the participants and ethical committee on time.

The duration of the research and the rules of research end point about six months.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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