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Safety of Direct Acting Antiviral Agents in Treatment of Chronic Hepatitis C and Thrombocytopenia

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Abstract

Background: Chronic hepatitis C virus infection is a leading cause of liver cirrhosis and associated with multiple extra hepatic complications including thrombocytopenia which may lead to serious bleeding. Also it may interfere or even prevent the initiation and continuation of antiviral therapy. A new direct-acting antiviral agents (DAAs) had been developed for treatment of chronic HCV infection.

Objective: Evaluating the safety, and efficacy of treatment with direct acting antiviral agents (DAAs) in treatment of chronic HCV infection and thrombocytopenia.

Patients and Methods: The study was conducted on 300 patients with chronic HCV infection, they were divided into 3 groups, group I included 100 patients with HCV and platelets count ≤50,000/cmm, group II included 100 patients with HCV and platelets >50,000 up to150,000/cmm, and group III included 100 patients with HCV and normal platelets(>150,000/cmm). All the patients received different regimens of DAAs therapy for 3 months.

Results : The current study included 300 patients with chronic HCV, after 12 weeks of treatment with DAAs, there was a significant improvement in platelets count, in group I, the median of platelets increased from 45 x10³ to be 46 x10³ with a range 44 - 49x10³ at the EOT with SVR reached to 98%. In group II, the median of platelets increased from 121,000 to be 132,000 with a range 113 - 152x10³ at the EOT, with SVR reached to 99%.

Conclusion: Use of direct acting antiviral agents (DAAs) in Patients with Chronic HCV infection and Thrombocytopenia is safe and tolerable.

Keywords: Direct-acting antivirals, Sofosbuvir, HCV, Platelets, Cirrhosis.

Introduction:

Chronic hepatitis C virus (HCV) infectionhas a significant global impact. According to the World Health Organization (WHO), there are 170-200 million peoples were infected with (HCV), corresponding to 3% of the world's total population.In Egypt the situation is a quite worse. Egypt has the highest prevalence of HCV in the world, reached to 14.7% in 2008**(1).**

The main sequelae of chronic HCV are liver cirrhosis, liver failure and hepatocellular carcinoma. Besides hepatic affection, chronic HCV is also associated with several extra hepatic complications including thrombocytopenia, which is considered a major problem, particularly in patients with advanced liver disease**(2)**. The risk of serious bleeding with severe thrombocytopenia can prevent invasive procedures including surgery. Thrombocytopenia can also increase the risk of variceal bleeding, and may interfere or even prevent the initiation and continuation of antiviral

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therapy, decreasing the probability of successful HCV treatment. High efficacy and safety of new DAAs represent a major breakthrough in the treatment of chronic hepatitis C. (DAAs) are new classes of drugs used to treat hepatitis C[(3)].

DAAs target specific steps in the (HCV) life cycle. DAAs have shorter treatment times, fewer side effects, and higher SVR rates than older drugs. DAAs directly inhibit the HCV replication cycle leading to dramatic improvement and a higher SVR. There are four classes of approved DAAs; NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors (non-nucleoside inhibitors and nucleotide inhibitors)[(4, 5)].

Patients and Methods:

The current study is a prospective study and was included 300 patients infected with chronic HCV, and associated with thrombocytopenia. They were received treatment with DAAS for 3 months duration started from January 2019 to December 2020. written consents were obtained by patients who agreed to participate in this study.

They were divided into 3 groups: Group I (100) patients had chronic HCV & with (platelets ≤50,000/cmm). Group II (100) patients had chronic HCV, with (platelets > 50,000 – up to 150,000/cmm). Group III (100) patients had chronic HCV, with normal platelets count from > 150,000 /cmm).

All patients were under the following inclusion criteria : (age >18years, HCV-RNA positivity by PCR). Patients were excluded if they had any of the following : extra hepatic malignancy, previous liver transplantation, pregnancy, serum albumin < 2,8 g/dl, serum bilirubin > 3mg/dl, HBsAg +ve). All the patients were subjected to full history taking, general examination, and full laboratory investigations: CBC with platelets count, INR, liver function tests, Quantitative PCR for HCV RNA by Real-Time Reverse Transcription-PCR (RT-PCR) using the Cobas Amplicor, TaqMan HCV assay version 2.0 (Roche Diagnostic Mannheim, Germany) (the lower detection limit was 15 IU/ml)., s.creatinine, alpha fetoproteins, and pregnancy test in females). And pelvi abdominal ultrasound. Different regimens of (DAAs) were used in the management of the patients in this study; these included sofosbuvir + daclatasvir, with or without ribavirin, and ombitasvir /paritaprevir /ritonavir (qurevo) + ribavirin, and also Sofosbuvir / velpatasvir (Velpa).

Statistical analysis:

Data were coded, entered, and processed on a computer using statistical packaged for the social science (version 22, 2013; IBM SPSS, IBM Software.Package for Statistical analysis, SPSS). P value less than or equal to 0.05 was considered the cut-off value for significance.

Results:

The current study included 300 patients with chronic HCV who were divided into three groups according to platelets count : Group I included 100 patients with platelets ≤ 50,000/cmm. Group II included 100 patients with platelets from >50,000 –up to 150,000 /cmm). Group III included 100 patients with platelets from > 150,000 /cmm). All were subjected for DAAs therapy.

Table (1); in group I, the number of male was 83 (83%), while female number was 17 (17%), with the mean age 54.8 ±12.6 years. In group II, the number of male was 80 (80%), while female number was 20 (20%), withthe mean age 52.6 ±14.7 years.

There was a statistically significant difference (p-value < 0.05) between studied groups as regard Hemoglobin and platelets count at the base line, but not WBCs (p - value > 0.05).

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Table (1): Demographic and Hematological parameters of studied groups at base line

Variables		**Group I (n = 100)**	**Group II (n = 100)**	**Group III (n = 100)**	**t. test**	**P-value**
Sex	Male	83 83%	80 80%	85 85%	$X^2 = 0.88$	0.643
	Female	17 17%	20 20%	15 15%		
Age	Mean	54.8	52.6	48.4	KW = 11.2	**0.004**
	±SD	12.6	14.7	13.6		
Hb (g/dl)	Mean	13.4	14.0	13.1	KW = 9.95	**0.007**
	±SD	2.2	1.6	2.0		
WBCx 10^3/cmm)	Mean	5.9	6.4	5.9	KW = 4.3	0.112
	±SD	2.5	2.2	2.3		
PLTs(x 10^3/cmm)	Mean	44.8	124.1	323.4	KW = 265.9	< **0.001**
	± SD	4.0	14.8	86.0		

WBCs : white blood cells; PLTs: platelets ; Hb : hemoglobin; SD :standard deviation. X^2 : Chi-square test.

p-value < 0.05 is significant. KW: Kruskal Willis test. p-value > 0.05 is non significant

Table (2) ;There was a statistically significant difference (p-value < 0.05) between studied groups as regard serum albumin, serum bilirubin, AST, ALT and creatinine, but not HCV- RNA level by PCR (p-value > 0.05). There was a statistically significance (p-value < 0.05) between liver cirrhosis, and normal liver with about 95 cirrhotic patients in group I, compared to 66 and 17 cirrhotic patients in group II and III respectively

Table (2): Liver and kidney function tests, HCV-RNA level, and U/S of the studied patients at base line

Variables		**Group I (n = 100)**	**Group II (n = 100)**	**Group III (n = 100)**	**t. test**	**P-value**
ALB (g/dl)	Mean	3.8	4.1	4.0	KW = 15.5	< **0.001**
	± SD	0.6	0.6	0.5		
Bilirubin (mg/dl	Mean	0.7	0.7	0.8	KW = 12.6	**0.002**
	± SD	0.3	0.3	0.2		
AST (U/L)	Mean	49.1	46.3	40.3	KW = 10.2	**0.006**
	± SD	32.1	23.4	26.5		
ALT (U/L)	Mean	53.3	52.1	44.1	KW = 8.9	**0.012**
	± SD	40.2	32.2	32.3		
Creatinine (mg/dl)	Mean	1.2	1.1	1.1	KW = 6.4	**0.04**
	± SD	0.3	0.1	0.1		
PCR (IU/ml)	Mean	1182356.3	1423514.0	1489506.4	KW = 0.018	0.991
	± SD	2468502.9	2688579.2	2781474.9		
Ultra sound	Normal Liver	5 5%	34 34%	83 83%	128.8	< **0.001**
	Liver Cirrhosis	95 95%	66 66%	17 17%	128.8	< **0.001**
	+Spleen	34 34%	19 19%	25 25%	5.9	0.052

PCR: polymerase chain reaction ; ALT: alanine aminotransferase; ALB: albumin ; AST: aspartate aminotransferase ; Creat : creatinine ; Bilir: bilirubin

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Table (3): Relationship between platelets count and liver cirrhosis in groups I and II

		Cirrhotic L. (n=161)	**Non cirrhotic L.** (n=39)	**t. test**	**P-value**
Platelets ($x10^3$/ul)	Median	50	119	MW = 1832.5	**< 0.001**
	IQR	45 – 131	110 – 140		

IQR : inter quartile range

Table (3);There was a statistically significant difference (p-value < 0.05) between cirrhotic and non-cirrhotic patients as regard post-treatment platelets count.

Table (4) : Change of Platelet count from base line to post-treatment count.

	Pre treatment		**Post treatment**	**t. test**	**P-value**
Platelets ($x10^3$ /cmm)	**Group I (n=100)**				
	Median	45	46	4190.5	0.046
	IQR	43 – 48	44 – 49		
	Group II (n=100)				
	Median	121	132.5	3904.	0.007
	IQR	112 – 138	113.3 - 152.5		
	Group III (n=100)				
	Median	345	340	4775	0.582
	IQR	246.3 – 400	245 – 396		

Table (4) ;Improvement in platelets count from base line showed a statistically significant difference compared to end of treatment count (p-value < 0.05) in group I and group II.

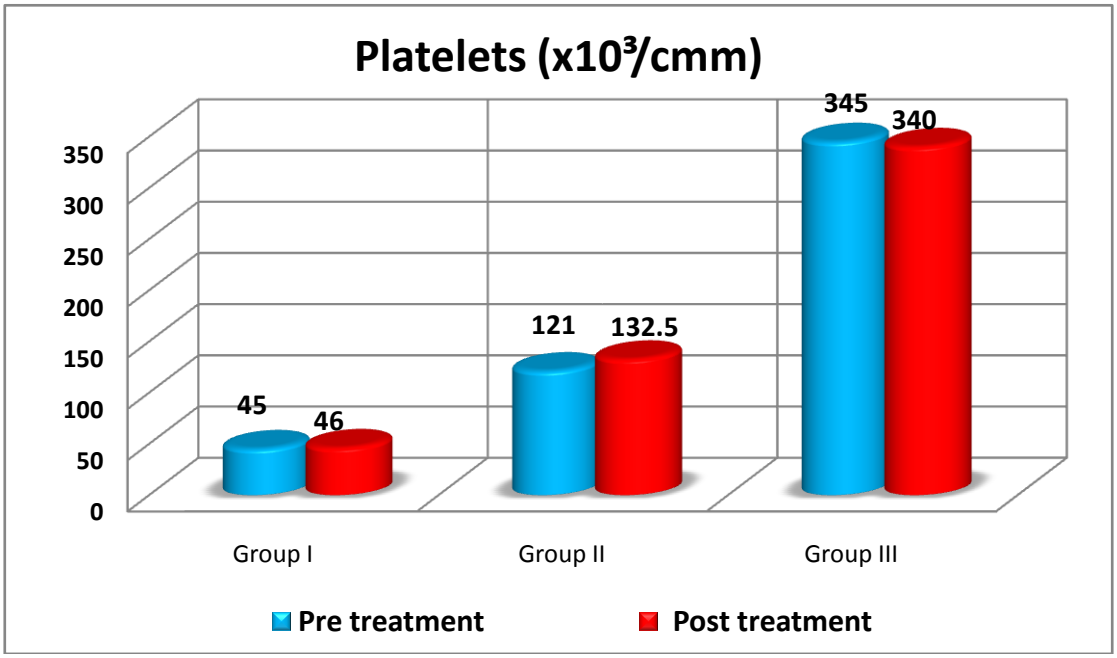

Figure (1): Improvement of Platelet count from base line to post-treatment count.

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Table (5): Relationship between End of treatment (platelets count and HCV vial load)

		Group I (n=100)	Group II (n=100)	Group III (n=100)	t- test	P-value
Platelets ($x10^3$/cmm)	Mean	46.3	142.6	317.7	KW = 262.5	< **0.001**
	±SD	3.8	101.0	86.4		
HCV- RNA	Negative	98 98%	99 99%	99 99%	$X^2 = 0.5$	0.776
	Positive	2 2%	1 1%	1 1%		

Table (5); There was no a statistically significant difference (p-value > 0.05) between studied groups as regard post-treatment HCV-RNA level and platelets count.

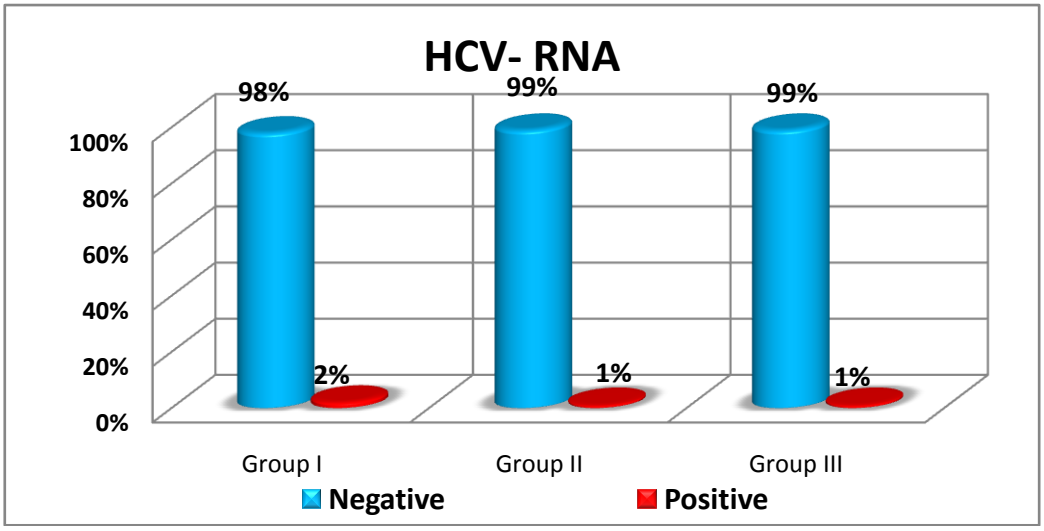

Figure (2): Sustained virological response to DAAs therapy in studied groups.

Table (6): Characteristics of studied patients with and without improvement of platelets count in group I

PLTs outcome			
		Improved (n = 43)	Not Improved (n =57)
Sex	Male	40 93%	43 75.4%
	Female	3 7%	14 24.6%
Age	IQR	50 – 62	47 - 65.5
Hb(g/dl)	IQR	10.9 – 15	11.3 - 15.4
WBCsx10^3	IQR	3.4 - 7.4	3.8 - 8
PLTsx10^3	IQR	39 – 48	45 - 48
ALB(g/dl)	IQR	3.4 - 4.1	3.5 - 4.25
Bil(mg/dl)	IQR	0.56 - 0.9	0.48 - 0.9
AST(U/L)	IQR	33 – 78	25 - 50.5
ALT(U/L)	IQR	36 – 77	24.5 -- 57
AFP(ng/ml)	IQR	3.9 - 8.9	4.35 - 9
DAAs	Dual	20	43
	Triple	19	11
	Qurevo	3	2
	Velpa	1	1

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Table (6);In group I, 43 patients showed improvement in platelets count most of them were male (93%), had elevated liver enzymes, and received Dual (20),Triple (19),Qurevo (3),and Velpa (1) Regimens of DAAs for treatment of HCV.

Table (7): Characteristics of studied patients with and without improvement of platelets count in group II

PLTs outcome			
		Improved (n = 55)	Not Improved (n = 45)
Sex	Male	47 85.5%	3373.3%
	Female	814.5%	12 26.7%
Age	IQR	45 – 64	37.5 - 65
Hb(g/dl)	IQR	13 – 15.6	12.8 - 14.7
WBCsx10^3	IQR	4.5 - 7.9	4.8 - 7.9
PLTsx10^3	IQR	119 – 143	110 – 123
ALB(g/dl)	IQR	3.6 - 4.3	3.7 - 4.7
Bil(mg/dl)	IQR	0.5 - 0.8	0.45 - 0.8
AST(U/L)	IQR	30 – 54	28 – 56.5
ALT(U/L)	IQR	30 – 81	30 – 62
AFP(ng/ml)	IQR	5.1 - 12.3	4.6 – 9
DAAs	Dual	40	35
	Triple	13	7
	Qurevo	2	3

Table (7);In group II, 55 patients showed improvement in platelets count most of them were male (85%), they had elevated liver enzymes, and received Dual (40), Triple (13), and Qurevo (2) regimens of DAAs for treatment of HCV.

Discussion:

The advanced and detailed understanding of the HCV genome and proteins was the hope that, encouraged efforts to improve efficacy and tolerability of HCV treatment, this led to the development of multiple direct acting anti virals (DAAs), they are medications targeted at specific steps within the HCV life cycle, that target specific nonstructural proteins of the virus and resulting in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanisms of action and therapeutic target. The NS5B polymerase inhibitor“ sofosbuvir ” was the first new DAAs approved for treatment of chronic HCV[(6)].

Chronic HCV infection is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Besides hepatic complications, chronic HCV infection is also associated with several extra hepatic manifestations including thrombocytopenia, which is considered a major problem. The risk of serious bleeding with severe thrombocytopenia can prevent invasive procedures including surgery, and can also lead to variceal bleeding. It may interfere or even prevent the initiation and continuation of antiviral therapy, decreasing the probability of successful HCV treatment [(7)].

There are many theories that may explain thrombocytopenia in patients with chronic HCV; HCV stimulates hepatic necroinflammation and fibrosis resulting in liver dysfunction and decreased production and activity of thrombopoietin. Also, HCV-mediated bone marrow inhibition and also the presence of auto antibodies causing immune thrombocytopenia [(8)].

Protocols for choice of HCV infected patients indicated for treatment with DAAs, according EASL guidelines [(9)], and to the Modified National Program for the treatment of HCV in Egypt

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(provided by the National Committee for Control of Viral Hepatitis (NCCVH) in 2014)**: (1) Easy to treat group:** receiving sofosbuvir and daclatasvir in cases of treatment-naive -total bilirubin< 1,2 mg\dl –S. albumin > 3,5 gm\dl - INR< 1,2 - Platelets count > 150,000 /cmm. **(2) Difficult to treat group:** receiving sofosbuvir, daclatasvir, and ribavirin**:** in cases of - Treatment-experienced - Total bilirubin >1,5 mg\dl - Serum albumin < 3,2 gm\dl - INR >1,2 – Platelets count < 100,000 and >50,000/cmm**(10)**.

The primary goal of treatment is to achieve a sustained virological response (SVR) (undetectable serum HCV RNA 12 weeks after the end of treatment) **(11 (12)**.

Several studies had investigated the relationship between HCV and platelet count before and after treatment with DAAs.

Aim of our study is to evaluate the relationship, safety and tolerability of treatment with direct acting anti-viral agents (DAAs) in Patients known to have Chronic Hepatitis C Virus Infection and Thrombocytopenia.

The current study included 300 patients, who were divided into three groups: group I included 100 patients with chronic HCV and platelets ≤ 50,000 /cmm. Group II included 100 patients with chronic HCV and platelets >50,000 – up to 150,000 /cmm). Group III included 100 patients with chronic HCV and platelets from > 150,000 /cmm). All were subjected for DAAs therapy.

In our study, we found that in the majority of the studied patients (HCV infected with thrombocytopenia),that were treated with DAAs regimens significantly improved platelet count at the end of treatment(EOT) compared to baseline, in groups I and II we found a significant difference **(p-value < 0.05)** in increasing in platelet count between pre-treatment and post treatment levels.

The results of our study were in agreement with the studies that conducted by**Welzelet al.(13)** and **Rafei et al.(14),**who founded a significant improvement in platelet count in the majority of patients after treatment of HCV with DAAs.

Also, the results of our study, were matched with that reported by**Mohamed et al. (15)**and **Hsu et al. (16),** who founded that there was a significant increase in the platelet count from week 2 until EOT in all patients with chronic HCV and thrombocytopenia.

The definite mechanisms of this platelets count improvement is still unclear and under investigation, however it is suggested that, the increased platelet count may be due to decreased sequestration of platelets in the spleen, lack of anti-platelets auto antibodies after eradication of HCV,**Aref et al. (17)** demonstrated the presence of these anti platelet antibodies in Chronic HCV patients. **De Almeida et al. (18)** and**Dai et al. (19)**, showed that HCV itself may be directly associated with decreased platelet counts. Therefore, the improvement of platelet count after the eradication of HCV is expected. Our study supports these suggestions that HCV produce anti platelet antibodies, or that HCV has a direct effect on platelets, therefore platelets count increased after treatment and complete eradication of chronic HCV.

Several previous multiple studies discussed the relationship between platelet count and chronic liver disease**.** In our study, we found that the relationship between platelet count and liver cirrhosis is inversely related, at the baseline, the platelet count is increased in patients with normal liver than that with liver cirrhosis by (U/S), which in group I with severe thrombocytopenia**,** liver cirrhosis represented about 95%**,** but in group III with normal platelets count, liver cirrhosis represented about 17%, these results were matchedwith **Osada et al. (20),** who observed significant differences in platelet count in different stages of liver disease and found a decrease in platelet count with the progression of hepatic fibrosis.

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Also these results of our study were agreed with **Kondo et al. [21]**,who reported that in patients with chronic hepatitis or cirrhosis platelet count significantly decreased with the severity of liver damage, so the more the liver damage and cirrhosis the more is the thrombocytopenia.

Multiple studies were conducted to assess and discuss different predictors and risk factors of response to treatment of chronic HCV with DAAs to achieve SVR. In our study, we investigated the effect of thrombocytopenia on the HCV viral load and it's response to treatment, we found that the majority of studied patients were responders at EOT and achieved SVR, and thrombocytopenia does not affect SVR, we found that, there was no a statistically significant difference between studied groups, as regard post-treatment HCV-RNA level detected by PCR and platelets count. In thrombocytopenic patients (groups I and II) the SVR was 98% and 99% respectively, also SVR in non-thrombocytopenic patients (group III) was 99%, with no a statistically significant difference between the overall patients. Our results were in accordance with the previously published data by **Mohamed et al. [15], Van der Meer et al.[22], and Lawitz et al. [23],** who found that most the studied patients were responders at EOT and achieved SVR. Additionally, sofosbuvir - based regimens significantly improved platelet count at EOT compared to baseline.

Also, the results of our current study were in agreement with **Zaghloulet al.[24]**, a study conducted on 260 patients known to have chronic HCV, that showed SVR and relapse in patients with thrombocytopenia didn't significantly differ from normal platelets patients.

Multiple previous studies were done to evaluate and identify the effect and relationship between platelet count and treatment of chronic HCV with DAAs regimens, most of these studies did not assess safety of DAAs with severe thrombocytopenia when platelet count ≤50,000 /cmm, most of guidelines, and also the Modified National Program for the treatment of HCV in Egypt (provided by the National Committee for Control of Viral Hepatitis (NCCVH) in 2014) : in difficult to treat group: receiving sofosbuvir, daclatasvir, and ribavirin: in cases of Platelets count < 100,000 and >50,000/cmm, and if platelets count ≤50,000 /cmm treatment was postponed and stopped. So one of the major challenges in treatment of chronic HCV is administration of DAAs therapy in cases of HCV and severe thrombocytopenia.

In the current study in group I, 100 patients with chronic HCV and severe thrombocytopenia platelet count ≤ 50,000 /cmm were received DAAs, then the results were analysed, as regard the deterioration of platelets count, safety of DAAs therapy on it, and the effect of severe thrombocytopenia on response at EOT.

In our study we found no significant decrease or deterioration of platelets count at the EOT, than the base line level as a side effect of DAAs regimens, in which if it had occurred it necessitates discontinuation of treatment, in the post treatment state,the median of platelets was 46, 132, 340 and the range was (44 - 49,113 - 152,245 - 396) in groups I, II, and III respectively. Our results were matched with the studies that had been evaluated the safety of DAAs with severe thrombocytopenia as**Zaghloul et al. [24]**, a study conducted on 260 patients known to have chronic HCV, and divided into 2 groups; group I included 60 patients with platelet count ≥150,000/mm3 as a disease control and group II (thrombocytopenia group) included 200 patients with platelet count ranged from 30,000- 149,000/mm3. Patients were subjected to DAAs that showed no a statistically significant difference in SVR, and no significant negative outcome on platelets count at the EOT.

This study has limitations, it did not follow-up the patients for long time after EOT to determine long-term outcomes, and the duration that the observed platelet count improvement may persist. Also larger studies for further investigation of the pathophysiology underlying this observation.

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Conclusion:

Thrombocytopenia is a complication of extra hepatic HCV- related liver disease. DAAs are a highly effective and safe regimens for treatment of chronic HCV. Patients with chronic HCV and have thrombocytopenia can be treated with DAAs safely and result in an improvement of platelet count at EOT. DAAs regimens are safe even if with severe thrombocytopenia.

References:

1. **WHO, (2014):** World Health Organization June "Hepatitis C". Retrieved, 2014- 07-13.
2. **El-Zanaty F, and Way A.(2009):** Egypt Demographic and Health Survey 2008.Egyptian Ministry of Health. El- Zanaty and Associates, and Macro International. Cairo. Egypt Demographic Health Survey: Final Report. Pp431.
3. **Abdel Ghaffar TY, El Naghi S, and Abdel Gawad M, et al (2019):**Safety and efficacy of combined sofosbuvir / daclatasvir treatment of children and adolescents with chronic hepatitis C genotype 4. J Viral Hepat.;26(2):263–270.
4. **Abergel A, Metivier S, Samuel D, Jiang D, Kersey K,and Pang PS, et al.,(2016)** : Ledipasvir plus sofosbuvir for 12 weeks in patients with genotype 4 infection. Hepatology; 64:1049–1056.
5. **Everson, K. D. Sims, and M. Rodriguez-Torres et al.,(2012):** An interferon-free, ribavirin-free 12-week regimen of daclatasvir (DCV), asunaprevir (ADV),and BMS-791325 yielded SVR4 of 94% in treatment-naïve patients with genotype(GT) 1 chronic hepatitis C viru (HCV) infection. Hepatology, 56: 3-6.
6. **Poordad F, Schiff ER,Vierling JM, Landis C, Fontana RJ, and Yang R, et al.(2016)**: Daclatasvir with sofosbuvir and ribavirin for HCV infection in advanced cirrhosis or post-liver transplant recurrence. Hepatology; 63:1493–1505.
7. **Kandeel A,Genedy M, El-Refai1 S, Funk A,Fontanet A, and Talaat M(2015)**:The prevalence of hepatitis C virus infection in Egypt: implications for future policy on prevention and treatment. Liver Int; 37:45–53.
8. **Saif - Al-Islam M, Mohamed HS, Younis MA, AbdelhamidMY, AliMM, and KhalafS. (2020):** Impact of gender difference on characteristicsand outcome of chronic hepatitis C. Open Journal of Gastroenterology, 10(11): 281–294.
9. **European Association for Study of Liver, (2015) :**EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatology, 63(1):199-236.
10. **Waked I, Doss W, El-Sayed MH, Estes C, RazaviH.,(2014) :**The current and future disease burden of chronic hepatitis C virus infection in Egypt. Arab J Gastroenterol.; 15 : 45– 52.
11. **Dufour JF, Zuckerman E, and Zadeikis N, et al.(2017)**: Safety of Glecaprevir/ Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection:An Integrated Analysis. Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver (EASL), Amsterdam, The Netherlands, 17: 19-23.
12. **Younossi ZM, Stepanova M,and Jacobson IM, et al. (2018):** Changes in patient Reported outcomes in direct acting antiviral - naïve chronic Egyptian Chronic Hepatitis C patients with Thrombocytopenia. International Journal of Science and Research, 6 (1): 321-327.
13. **Welzel TM, Petersen J, and Herzer K, et al., (2016)**:Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut;65:1861–70.

14. **Rafei H, Ascensao JL, and AggarwalA.,(2016):** Platelet count increase seen with ledipasvir–sofosbuvir combination treatment of chronic hepatitis C in patients with thrombocytopenia. Blood.; 128(22):5967–5967.

15. **Mohamed MS, Hanafy AS, Bassiony MA, and Hussein S. (2017):**Sofosbuvir, and daclatasvir plus ribavirin treatment improve liver function Parameters and clinical outcomes in Egyptian chronic hepatitis C patients. European Journal of Gastroenterology &Hepatology, 29(12): 1368 –1372.

16. **Hsu WF, Lai HC, and Su WP et al.,(2019):**Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct acting antiviral agents. BMC Gastroenterology,19(1): 63–75.

17. **Aref S, Sleem T, and El Menshawy N, et al.,(2009)**:Antiplatelet antibodies contributeto thrombocytopenia associated with chronic hepatitis C virus infection. Hematology, 14:277–81.

18. **De Almeida AJ, Campos-de-Magalhaes M, and de MeloMarcal OP, et al.,(2004):**Hepatitis C virus-associated thrombocytopenia: a controlled prospective, virological study. Ann Hematol., 83:434–40.

19. **Dai CY, Ho CK, and Huang JF, et al.,(2010):**Hepatitis C virus viremia and low platelet count: a study in a hepatitis B & C endemic area in Taiwan. J Hepatol;52:160–6.

20. **OsadaM.,Kaneko M., and Sakamoto M. et al.,(2012):**Causes of thrombocytopenia in chronic hepatitis C viral infection. Clinical and Applied Thrombosis/Hemostasis, 18(3): 272–280.

21. **Kondo R,Yano H,Nakashima O,Tanikawa K, Nomura Y, and Kage M.(2012):** Accumulation of platelets in the liver may be an important contributory factor to thrombocytopenia and liver fibrosis in chronic hepatitis C. Journal of Gastroenterology, 48(4): 526–534.

22. **Van der Meer AJ, Maan R, Veldt BJ, et al.(2016) :** Improvement of platelets after SVR among patients with chronic HCV infection and advanced hepatic fibrosis. J GastroenterolHepatol;31:1168–76.

23. **Lawitz E, Poordad F, Wells J, Hyland RH, Yang Y and, Dvory-Sobol H. (2017):**Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus. Hepatology; 65 (6): 1803–1809.

24. **Zaghloul SG, Hammam AA, Wadea FM, and Saeed MR. (2015):** Outcome of Sofosbuvir Containing Treatment Regimens in Egyptian Chronic Hepatitis C Patients with Thrombocytopenia. International Journal of Science and Research; 6: 321- 327.