



Hematological Changes in HCV Patients Treated with Different Sofosbuvir-Based Regimens

**Ahmed Abdel Khalek¹, Abdel Raouf El-Deib¹, Gamal Tawfik¹, Nashaat Soliman²
and Mohamed Mosaad^{2*}**

¹*Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Egypt.*

²*Department of Endemic and Infectious Diseases, Faculty of Medicine,
Suez Canal University, Egypt.*

Authors' contributions

This work was carried out in collaboration among all authors. All Authors shared designing the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Treatment of HCV with direct acting antiviral agents (DAAs) with the different regimen dramatically changed the outcomes of the disease beside its eradication. In the same time hematological concerns as anemia, thrombocytopenia, and leucopenia were a major factor before initiation, or during treatment with the antiviral drugs.

Aim: To demonstrate hematological changes during and after treatment with different regimen of DAAs.

Methods: Follow up the hematological changes before, during and after treatment for 100 patients with chronic HCV treated with five different sofosbuvir-based regimen; using interferon, ribavirin, simeprevir and daclatasvir.

Results: There are no similar linear changes regarding anemia, leucopenia or thrombocytopenia, however, combination therapy using sofosbuvir with simeprevir or daclatasvir significantly increase platelets count, WBCs, and hemoglobin level during and after end of treatment, versus regimens

*Corresponding author: Email: mohmosad4@yahoo.com;

uses sofosbuvir with ribavirin and or interferon that showed significantly decreased hematological values during and after treatment.

Conclusion: Sofosbuvir-based regimen has favorable hematological changes in patients with chronic HCV infection during and after treatments especially with sofosbuvir and daclatasvir.

Keywords: DAAs; HCV; Hematological changes.

1. INTRODUCTION

HCV management is a major concern in Egypt and other endemic countries [1,2]. Until few years ago, this depended largely on combination therapy with interferon and ribavirin, which did not give SVR (sustained virological responses) more than 50%-70% in all the virus genotypes; besides many side effects recorded and resulted in discontinuations of treatment [3,4]. Hematological side effects as anemia, neutropenia, and thrombocytopenia always recorded in guidelines as reasons to stop treatment either temporarily or permanently, and this negatively affected the response to treatment [5]. Recently the emerging of the new direct antiviral drugs as, Sofosbuvir, Simeprevir, Daclatasvir and Velpatasvir, dramatically changed the outcomes of treatment where SVR reached 100% in some combinations [6], moreover, some reported milder side effect compared to old treatment. The new combinations contain Sofosbuvir, which is a uridine nucleotide analogue that selectively inhibits the HCV NS5B RNA-dependent RNA polymerase. It targets the highly conserved nucleotide binding pocket of this enzyme and functions as a chain terminator [7]. The new DAAs drugs have been introduced to the protocols in Egypt with the old drugs in different combinations, and the Ministry of Health approved these and started to use them in the centers which deals with the patients for HCV. This study aimed to demonstrate hematological changes during and after treatment with different regimen of DAAs.

2. SUBJECTS AND METHODS

We compared five different matched groups of adult patients suffering chronic hepatitis C virus infection treated by different regimens containing Sofosbuvir in the hepatic center of Ismailia fever hospital.

2.1 Inclusion Criteria

1-Adult patients with chronic hepatitis C virus infection treated by sofosbuvir-based regimen. 2-

Male or female patients between 18 and 70 years old.

2.2 Exclusion Criteria

1-Patients suffering co-morbidities or chronic illnesses other than chronic hepatitis c virus infection such as hepatitis B virus infection, human immunodeficiency virus infection, autoimmune disease or renal failure. 2-Patients with chronic hepatitis C who are not candidates for sofosbuvir based treatment regimen. 3-Patients with primary hematological diseases such as thalassemia, idiopathic thrombocytopenic purpura (ITP), leukemia or chronic blood loss. 4-Patients taking oral or parenteral hematopoietic stimulating agents as oral iron preparations and erythropoietin.

2.3 Study Method

Five groups had been monitored; we did not interfere in the choices for the consultants to use any combination; and we included in the study the first 100 hundred patients matching our inclusion and exclusion criteria blindly and tabulated them according to the regimen they used. The first group included 30 patients treated by triple therapy of sofosbuvir, ribavirin and interferon for three month duration. The second group included 20 patients treated by dual therapy of sofosbuvir and ribavirin for six month duration. The third group included 20 patients received dual therapy of sofosbuvir and semiprevir for three months. The fourth group included 15 patients received triple therapy of sofosbuvir, daclatasvir and ribavirin for three months and the last group included 15 patient received sofosbuvir and daclatasvir only for three months. The following data were collected: A- History and physical examination. B- Complete blood picture and reticulocytic count. C- Tests for hepatitis B and C viruses. D- Evaluation of renal, hepatic and coagulation functions. E- Abdominal ultrasound. All these data recorded before, during all the treatment course duration and for three months after treatment. Finally, the hematological profile as Hb level, platlet count, and leucocytic count before, at the middle and end of treatment were recorded and compared.

2.4 Data Analysis

The data obtained from the patients coded, organized and the final study results stated using the SPSS version 16 and data presented through tables and graphs. Data were compared by using Chi-square and independent t-tests used for test for qualitative and quantitative variables. Statistical significance is considered at P-value < 0.05 and highly significant at P-value < 0.01. a regression models made for all the variables that affect the haematological pictures.

3. RESULTS

For regimen 1 using sofosbuvir with interferon and ribavirin (Fig. 1), the mean haemoglobin concentration before treatment was 13.6 ± 1.6 g/dL. This dropped to 12.1 ± 1.7 g/dL during treatment that fell to 11.2 ± 1.5 g/dL after treatment. Mean total leukocytic count before treatment was 5.0 ± 1.5 x1000/dL. This fell down towards 4.5 ± 1.4 x1000/dL during treatment that fell again to 3.8 ± 1.4 x1000/dL after treatment. Mean platelet count before treatment was 154.9 ± 62.6 x1000/dL. This fell down towards 140.1 ± 45.2 x1000/dL during treatment that fell again to 125.3 ± 39.9 x1000/dL after treatment. The differences between measurements before, during and after treatment course were all of highly statistically significant difference. For regimen 2, which contained sofosbuvir and ribavirin only (Fig. 2), the mean haemoglobin concentration before treatment was 12.2 ± 1.6 g/dL. This was reduced to reach 11.7 ± 2.0 g/dL during treatment that fell to 11.4 ± 2.1 g/dL after treatment; The differences between haemoglobin concentration before and during treatment and before and after treatment was the only statistically significant. Mean total leukocytic count before treatment was 5.4 ± 1.6 x1000/dL. This fell down towards 5.0 ± 1.5 x1000/dL during treatment that kept at 5.0 ± 1.7 (raised SD) x1000/dL after treatment. Mean platelet count before treatment was 121.3 ± 39.2 x1000/dL. This fell down towards 109.6 ± 39.0 x1000/dL during treatment that fell again to 105.4 ± 39.8 x1000/dL after treatment. In regimen 3 which included the dual therapy of sofosbuvir and simeprevir (Fig. 3) the mean haemoglobin concentration before treatment was 12.565 ± 1.662 g/dL. This was increased to reach 12.84 ± 1.871 g/dL during treatment that increased to 13.62 ± 2.394 g/dL after treatment. Mean total leukocytic count before treatment was 6.455 ± 1.833 x1000/dL. This rose towards 6.71 ± 1.904

x1000/dL during treatment that rose to 7.31 ± 1.707 (raised SD) x1000/dL after treatment. Mean platelet count before treatment was 182.05 ± 58.541 x1000/dL. This rose towards 195.4 ± 68.953 x1000/dL during treatment that rose again to 216.95 ± 65.922 x1000/dL after treatment. In regimen 4 which included sofosbuvir, daclatasvir and ribavirin (Fig. 4) the mean haemoglobin concentration before treatment was 12.453 ± 1.34 g/dL. This was reduced to reach 12.24 ± 1.24 g/dL during treatment that rose to 12.507 ± 1.234 g/dL after treatment. Mean total leukocytic count before treatment was 5.873 ± 2.027 x1000/dL. This rose up towards 6.36 ± 1.557 x1000/dL during treatment that rose again to reach 6.44 ± 1.282 (raised SD) x1000/dL after treatment. Mean platelet count before treatment was 183.73 ± 83.421 x1000/dL. This rose towards 186.93 ± 77.354 x1000/dL during treatment that rose again to reach 203.07 ± 80.487 x1000/dL after treatment, however, The differences in between platelet count only before and during treatment and before and after treatment were statistically significant. In regimen five which contained sofosbuvir and daclatasvir only (Fig. 5), the mean haemoglobin concentration before treatment was 11.627 ± 1.65 g/dL. This rose to reach 11.773 ± 1.299 g/dL during treatment that rose again to 12.48 ± 1.538 g/dL after treatment. Mean total leukocytic count before treatment was 5.493 ± 1.29 x1000/dL. This rose towards 5.58 ± 1.145 x1000/dL during treatment that rose again to reach 6.313 ± 1.351 x1000/dL after treatment. Mean platelet count before treatment was 183.6 ± 80.004 x1000/dL. This rose towards 190.4 ± 77.285 x1000/dL during treatment that rose again to 204.8 ± 77.867 x1000/dL after treatment; The differences between haemoglobin concentration before and during treatment and before and after treatment was statistically significant, same as the differences between platelet count before and during treatment and before and after treatment. Table 1 shows that the variables that mostly contributed significantly to the haemoglobin change were the constant, Haemoglobin, the regimen used and the presence of splenomegaly. Table 2 shows that the variables that mostly contributed significantly to the total leukocytic count change were total leukocytic count, the regimen used and the presence of splenomegaly. Finally, Table 3 shows that the variables that mostly contributed significantly to the platelet count change were platelet count, the constant, the regimen used and the presence of splenomegaly.

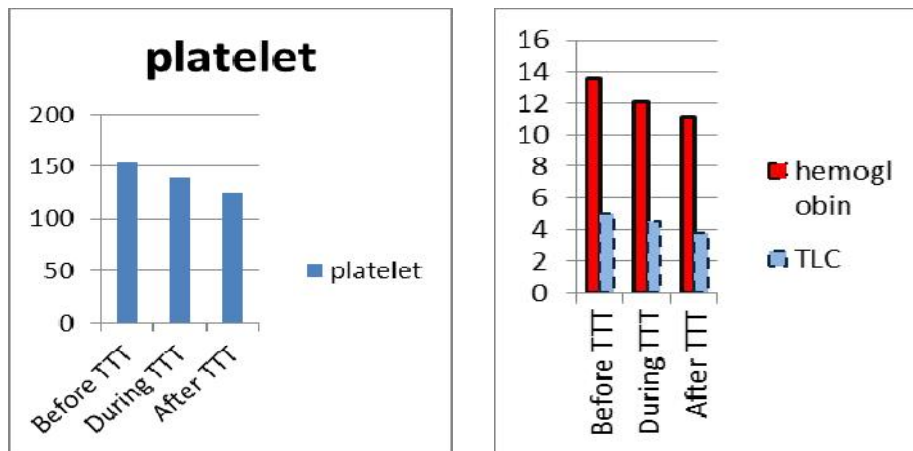


Fig. 1. Shows changes in Hb, total leucocytic count (TLC) and platelet counts in patients received Sofosbuvir, Interferon and Ribavirin

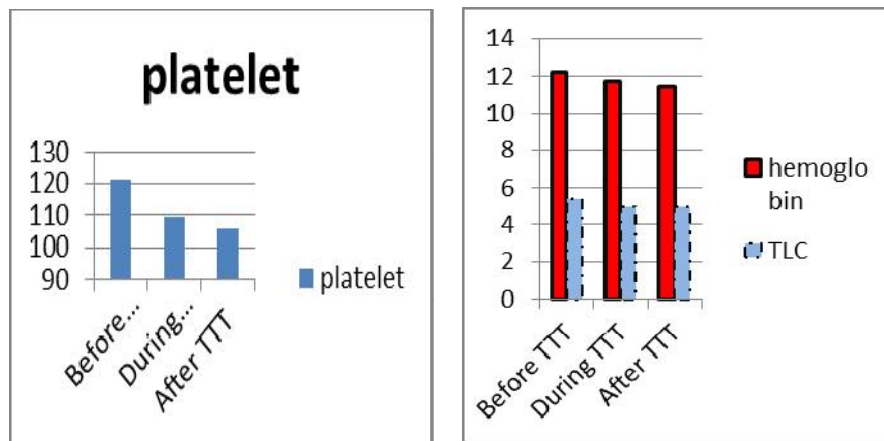


Fig. 2. Shows changes in Hb, total leucocytic count (TLC) and platelet counts in patients received Sofosbuvir and Ribavirin

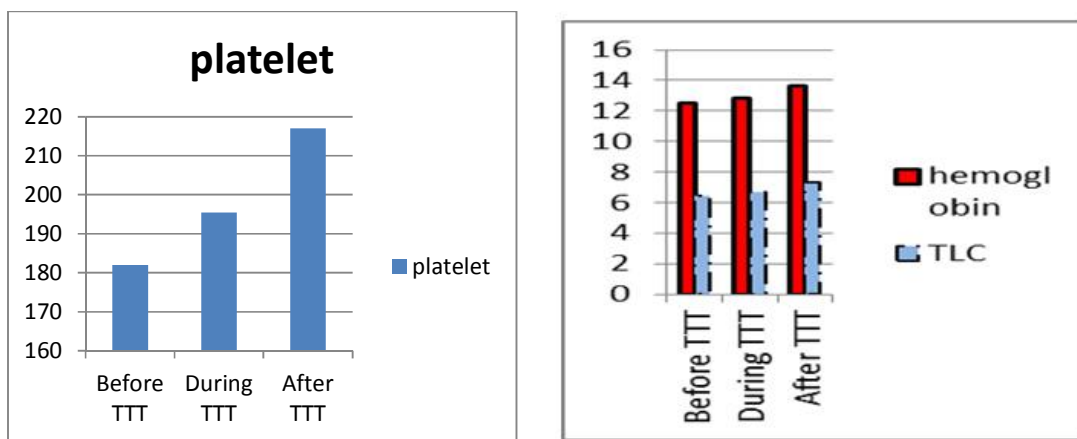


Fig. 3. Shows changes in Hb, total leucocytic count (TLC) and platelet counts in patients received Sofosbuvir and Simeprevir

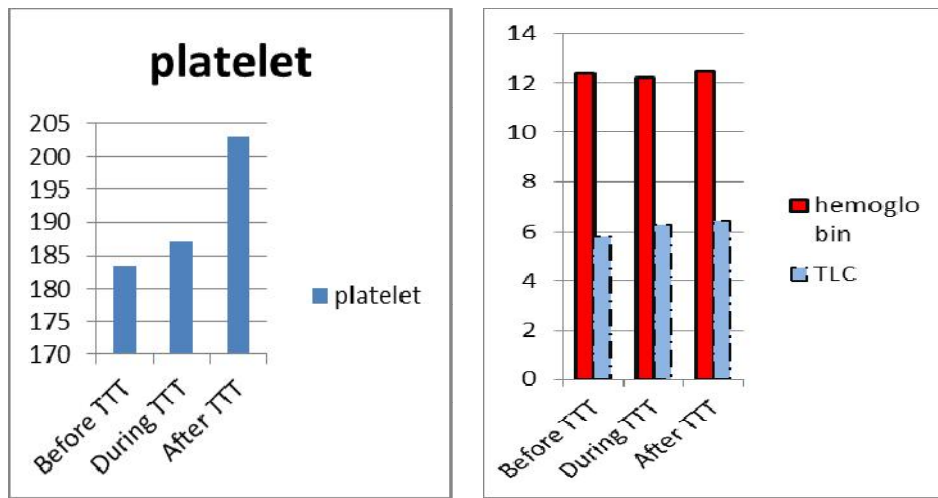


Fig. 4. Shows changes in Hb, total leucocytic count (TLC) and platelet counts in patients received Sofosbuvir, Daclatasvir, and Ribavirin

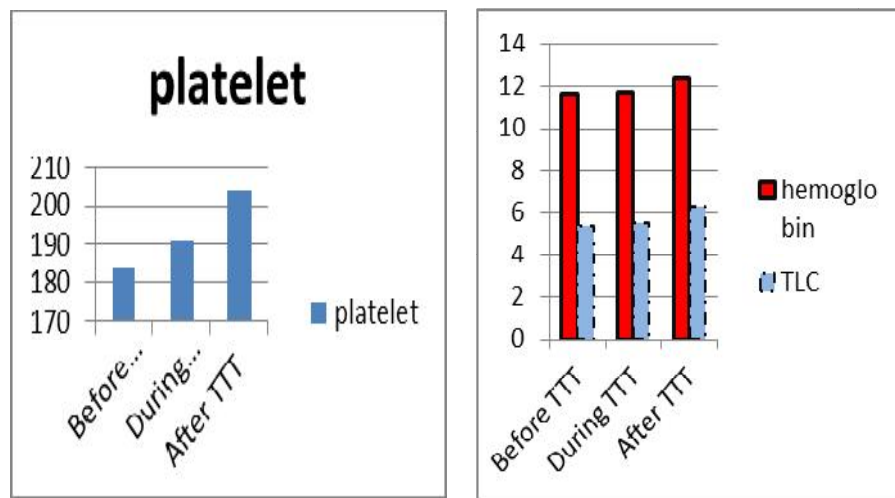


Fig. 5. Shows changes in Hb, total leucocytic count (TLC) and platelet counts in patients received Sofosbuvir and Daclatasvir

Table 1. Coefficients of haemoglobin change regression model

	Unstandardized Coefficients	t	p-value	95.0% Confidence Interval for B	
	B			Lower Bound	Upper Bound
(Constant)	2.261	3.007	0.003	.768	3.754
Haemoglobin (g/dL)	-0.074	-2.032	0.045	-0.146	-0.002
Regimen	0.154	3.342	0.001	.062	0.245
Age	-0.002	-0.252	0.801	-0.015	0.011
Sex	-0.141	-1.249	0.215	-0.365	0.083
Diabetes mellitus	0.053	.266	0.791	-0.340	0.446
Splenomegaly by U/S	-0.408	-3.434	0.001	-0.643	-0.172

Table 2. Coefficients for leukocytic count change regression model

	Unstandardized Coefficients	t	p-value	95.0% Confidence Interval for B	
	B			Lower Bound	Upper Bound
(Constant)	0.867	1.650	0.102	-0.176	1.909
Regimen	0.128	2.640	0.010	0.032	0.224
Age	0.010	1.334	0.186	-0.005	0.025
Sex	0.164	1.371	0.174	-0.073	0.401
Diabetes mellitus	-0.172	-0.759	0.450	-0.622	0.278
Splenomegaly by U/S	-0.392	-2.764	0.007	-0.674	-0.110
Total leukocytic count (x1000/dL)	-0.088	-2.352	0.021	-0.163	-0.014

Table 3. Coefficients for platelet count change regression model

	Unstandardized Coefficients	t	p-value	95.0% Confidence Interval for B	
	B			Lower Bound	Upper Bound
(Constant)	1.883	4.814	<0.0001	1.106	2.660
Regimen	.152	4.100	<0.0001	.079	0.226
Age	-0.006	-0.986	0.327	-0.017	0.006
Sex	0.032	0.353	0.725	-0.149	0.214
Diabetes mellitus	0.043	.247	0.806	-0.304	0.391
Splenomegaly by U/S	-0.302	-2.467	0.015	-0.544	-0.059
Platelets (x1000/dL)	-0.002	-2.712	0.008	-0.004	-0.001

4. DISCUSSION

This study included 100 patients diagnosed as having hepatitis C virus infection, by HCV antibody and PCR. All patients suffered compensated disease and were allowed to start 5 different antiviral regimens at the hepatic center of Ismailia fever hospital in Ismailia, Egypt. The main hematological changes that observed involve hemoglobin, platelet count and total leucocyte counts. Our results showed, in the logistic regression model, that the variables that mostly contributed significantly to these hematological changes were the regimen used and the presence of splenomegaly, which actually present in 68% of our patients, and this may reflect that the regimen used was a major significant factor in these changes.

Regarding group one who received sofosbuvir with ribavirin and interferon, levels of hemoglobin, total leucocyte count and platelet count decreased during treatment and continue to decrease at the end of treatment, where the change in these levels was significant when compared before and after treatment. This is

near to other studies [4,8,9,10], where side effects of IFN- α and PEG-IFN- α , resulted in bone marrow suppression, leading to anemia and neutropenia [8]; this anemia mostly is dose-dependent haemolytic anemia when using ribavirin [4]; in another study, When combination therapy with IFN- α /Rbv is used, hemoglobin levels <11 g/dL occur in 25%–30% of patients and, the incidence of dose modifications, due to anemia, increased from 0% with IFN- α monotherapy, to 7%–9% with combination therapy [9]. In addition, dose reductions due to neutropenia and thrombocytopenia were more common when using PEG-IFN- α /ribavirin therapy than with standard IFN- α /ribavirin therapy [10].

For regimen 2 which contained sofosbuvir and ribavirin only, the results showed that the levels of hemoglobin decreased by a significant difference during and at the end of treatment course. While the total leucocytic count and platelet count continue to decrease during and at the end of the course, but these were statistically insignificant; so in absence of interferon, these changes also can be caused by ribavirin as mentioned in regimen1. This also reported in

another study as sofosbuvir does not appear to worsen anemia when combined with ribavirin nor decreased, white blood cell or platelet counts. In contrast to interferon-containing regimens [11].

In regimen 3, using sofosbuvir and simeprevir there was continuous increase in measurements of haematological parameters during and after treatment as compared to those before treatment. The differences in between haemoglobin concentration before and during treatment and before and after treatment was statistically significant, same as the differences in between platelet count before, and during treatment, and before and after treatment. This may be partly due to absence of ribavirin and interferon, and partly may be due to positive effects for sofosbuvir and simeprevir.

In regimen 4 which included sofosbuvir, daclatasvir and ribavirin, there were continuous increase in measurements of haematological parameters during and after treatment as compared to those before treatment with statistical significant differences in platelets counts. But the positive effects for sofosbuvir and daclatasvir did not appear to be of statistical significance because of the negative effect for ribavirin. But when we used this combination in regimen 5 without ribavirin, The differences between haemoglobin concentration before and during treatment and before and after treatment was statistically significant, same as the differences between platelet count before and during treatment and before and after treatment. However, total leukocytic count showed a mild increase first followed by a mild decrease which was insignificant. This is near to what we found in ALLY-3 trial, where 152 treatment-naïve and treatment-experienced subjects with HCV genotype 3 infection were treated with dclatasvir in combination with sofosbuvir [12]. The safety and beneficial effects of sofosbuvir not only confined to the combinations we used as with what reported with daclatasvir [13], but also reported in other combinations as with velpatasvir [14], and moreover this safety and beneficial effects have been found in special difficult to treat cases [15]. For patients suffering compensated chronic hepatitis C virus infection and received treatment by regimens containing sofosbuvir combined with interferon or ribavirin or both together, there was a significant decrease in the levels of hemoglobin, total leucocytic count and platelet count before and after treatment. This decrease involved one, two, or even the three levels together. On the other hand, when

sofosbuvir given in combination without interferon or ribavirin, there was no observed significant decrease in the levels of hemoglobin, total leucocytic count and platelet counts during treatment. Moreover, these levels showed significant improvement at the end of treatment when combined with simeprevir or daclatasvir. However the changes in hemoglobin, platelets counts, and leucocytic count were not similar or linear pattern in the same drug regimen in every group. But these changes and responses may need larger sample size to be more emphasized.

5. CONCLUSION

sofosbuvir-based regimen in chronic hepatitis C patients showed improvement for the dilemma of anemia and thrombocytopenia in those patients even in presence of ribavirin, but better with simeprevir or daclatasvir. DAAs alone have no passive effect on the hematological pattern in chronic hepatitis C virus infection, and after cure from the disease, the hematological pattern is likely to improve if compared to that before treatment.

CONSENT AND ETHICAL APPROVAL

This search was approved, by the ethical committee, in Faculty of Medicine, Suez Canal University. Oral consent was taken from every patient, and we did not interfere in the decision for the suitable regimen for every patient.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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