Acta Scientific Gastrointestinal Disorders

Volume 1 Issue 2 October 2018

Research Article

Adding Ribavirin to Sofosbuvir/Daclatasvir Treatment Regimen for Chronic Hepatitis C Patients. Cost Effective Analysis

Ehab Kamal[1]*, Mohamed Abdallah[1], Hazem M El-Hariri[2], Soheir Ismail[3], Kadry El Saeed[4] and Yehia El Shazly[4]

[1]*Medical Research division, National Research center, Giza, Egypt*

[2]*Community Medicine Research Department, National Research center, Giza, Egypt*

[3]*Department of Tropical Medicine, National Hepatology and Tropical Medicine and Research Institute, Cairo, Egypt*

[4]*Internal Medicine Department, Ain Shams University, Cairo, Egypt*

***Corresponding Author:** Ehab Kamal, Medical Research division, National Research center, Giza, Egypt.

Received: September 12, 2018; **Published:** October 14, 2018

Abstract

Background: Ribavirin has been considered a corner stone drug in Hepatitis C treatment for a long time, recently with the introduction of direct acting antivirals. Ribavirin remains to have a limited role in new treatment regimens. This study is a comparative cost effective study between Sofosbuvir/Daclatasvir/Ribavirin regimen for 12 weeks versus Sofosbuvir/Daclatasvir for 24 weeks.

Methods: A comparative prospective study is done involving 231 chronic experienced Hepatitis C patients. The patients were randomized in to 2 groups; Group (A) treated by Sofosbuvir/Daclatasvir/Ribavirin for 12 weeks and Group (B) treated by Sofosbuvir/Daclatasvir for 24 weeks. Cost effectiveness analysis assessed the benefit of using ribavirin instead of extending the treatment period regarding sustained virologic response rates, Side effects and financial cost.

Results: Group (B) showed a "non-significant" higher sustained virologic response rates than group (A) 93.7% versus 92.5%. Anemia was the most reported side effects in group (A) however; it was easily controlled in all patients with RBV dose reduction. Group (A) treatment cost nearly the half of Group (B). 3914 versus 5753 Egyptian pounds.

Conclusion: Analysis of the data favors the beneficial effect of using ribavirin regarding sustained virologic response rates, Side effects and financial cost.

Keywords: Ribavirin; Hepatitis C Virus; Direct Acting Antivirals; Cost effectiveness; Sofosbuvir/Daclatasvir

Abbreviations

AFP: Alpha Feto Protein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; *B*-HCG: Beta Human Chorionic Gonadotropin Test; Bil: Serum Bilirubin Levels; CBC: Complete Blood Count; DAAs: Direct Acting Antivirals; DCV: Daclatasvir; EGP: Egyptian Pounds; HbsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; IFN: Interferon; NCCVH: The National Committee for Control of Viral Hepatitis; PCR: Polymerase Chain Reaction; RBV: Ribavirin; SE: Side Effects; SOF: Sofosbuvir; SVR: Sustained Virological Response

Introduction

Hepatitis C infection (HCV) is a major health problem, infecting approximately 170 million people worldwide [1]. The majority of infected patients develop chronic infection, which may lead to liver cirrhosis, hepatocellular cancer and death [2]. Approximately 350,000 to 500,000 people die each year from hepatitis C-related complications around the world [3]. Egypt is the country with the highest HCV prevalence in the world. It is estimated that - in the (1 - 59 year) age group - 5.3 million persons are positive for HCV antibodies and, of these, approximately 3.7 million (69.5%) are HCV RNA positive [4].

Direct-acting antiviral agents (DAAs) have revolutionized the treatment of chronic HCV infection [5]. Compared with peg interferon and ribavirin dual therapy, regimens including a DAA showing higher efficacy with shorter treatment durations and low incidence of adverse events [6]. Recently, most recent guidelines recommend using Interferon (IFN) - Free DAA regimens, however using a ribavirin is still an option for treatment [7].

According to recent guidelines of the national committee for control of viral hepatitis (NCCVH) - Ministry of health, Egypt. We can use Sofosbuvir (SOF)/Daclatasvir (DCV)/Ribavirin (RBV) for 12 weeks or SOF/DCV for 24 weeks treatment for treatment experienced patients [8].

The treatment program done my NCCVH has succeeded in treatment over 1.5 million patients since the introduction of DAAs. In 2015, the seroprevalence of HCV infection in Egypt has declined to 6.3% with an overall estimated 30% decrease in HCV prevalence in Egypt between 2008 and 2015 [9]. This success came with a huge financial cost on the government, which necessitates starting cost reduction studies in multiple aspects of our Egyptian HCV model of care.

So, in our study we aim to analyze to cost effectiveness of using ribavirin instead of doubling the treatment period. Issues of sustained virological response (SVR) rates, Side effects, and financial cost of both regimens will be evaluated to determine which regimen is better to use especially in low and middle income countries.

Materials and Methods

Patients and study design

Enrolment was done to 231 HCV patients who were treated within the treatment centers of the national committee for control of viral hepatitis (NCCVH). All these patients were treatment experienced. The patients were randomly divided into two groups; Group (A) contains 120 patients received the treatment regimen of Sofosbuvir 400 mg, Daclatasvir 60 mg, in addition to a "weight based" Ribavirin regimen for 12 weeks, And Group (B) contains 111 patients received the treatment regimen of SOF/DCV for 24 weeks.

Inclusion criteria

1- Patients positive for HCV RNA.
2- Age more than 18 years old, patients above 65 years old will undergo full cardiological assessment.
3- Treatment experienced patients.

Exclusion criteria

1- Child C patients.
2- Platelet count less than 50000 per mcL.
3- Hepatocellular carcinoma except after 6 months of successful intervention.
4- Extra hepatic malignancy except after 2 years of disease free interval except for lymphoma or chronic lymphocytic leukemia after remission according to recommendation of oncologist.
5- Pregnancy or inability for successful contraception.

All enrolled patients will be exposed to:

- All patients signed an informed consent about the study and they were informed to have full right to discontinue the study at any time without stopping his treatment course, then the patient is randomized into the 2 previously mentioned groups.
- Careful history taking and medication history.
- Full clinical examination.
- All the patients before enrolment will be exposed to the following investigations: Complete blood count (CBC), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Serum Bilirubin levels (Bil), Serum albumin, Serum creatinine, Bleeding profile, Alpha feto protein (AFP), And hepatitis B surface antigen (HBsAg),
- For the female patients Beta Human Chorionic Gonadotropin test (β-HCG) will be done to exclude pregnancy.
- Pelviabdominal ultrasound will be done for all the patients.
- Quantitative HCV Polymerase Chain reaction (PCR).

Monthly follow up visits was done containing medical examination, Side effects (SE) reporting and laboratory investigations "CBC, ALT, AST, Bil, Creatinine".

Sustained virological response (SVR) was evaluated by PCR after 12 weeks of the end of the treatment.

Side effects were recorded all over the study duration and the cost effectiveness studies were evaluated after the SVR.

The cost effectiveness comparison between the two groups will evaluate the best treatment option for this group of patients concerning economic burden, compliance, and side effects, in addition to the indirect costs such as transportations and work absenteeism during visits.

The total expenses were measured to include Drug cost, Medical supervision fees, laboratory investigations and pelviabdominal ultrasound. All expenses will be expressed in Egyptian pounds (EGP). EGP equals 0.56 united stated Dollar Approximately.

All the used drug are Egyptian licensed generic versions of DAAs.

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables using independent t-test. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

Results

In the present study; 231 patients were involved with chronic HCV infection eligible for antiviral treatment. All of them are treatment experienced patients. Study demographics showed a slight female predominance in both groups, mean age in group A and B was 49.9 and 51.6 respectively (Table 1).

		Group A (N = 120)	Group B (N = 111)	P
Sex	Male	40 (33.3%)	47 (42.3%)	#0.158
	Female	80 (66.7%)	64 (57.7%)	
Age (years)	Mean ± SD	49.9 ± 11.4	51.6 ± 10.8	^0.166
	Range	18.0 - 75.0	20.0 - 75.0	

Table 1: Demographic data of the patients.

#: Chi square test.

Regarding the SVR in group (A) the SVR was seen in 111 patients representing 92.5% of the total patients, while in group B the SVR rates was seen in 104 patients representing 93.7% of the total group. There is no significant difference regarding the SVR between the two groups (Table 2).

		Group A (N = 120)	Group B (N = 111)	P
Sustained virological response	Negative	111 (92.5%)	104 (93.7%)	#0.721
	Positive	9 (7.5%)	7 (6.3%)	

Table 2: SVR rates among the two groups.

#: Chi square test.

There was no statistically significant changes in baseline labs between both groups. Side effects (SE) related to ribavirin was mainly expressed in the form of Anaemia, no other SE was reported.

In group A, Hemoglobin significantly decreased at week-4, and then continued to decrease at week-8, finally reincreased at week-12 but still significantly lower than the basal. Most of reductions occurred at week-4 (Table 3).

Hemoglobin levels (gm/dL)			
Time	**Mean ± SD**	**Range**	**P**
Basal	12.9 ± 1.5	10.2 - 17.1	^< 0.001*
Week-4	11.6 ± 1.5	7.0 - 14.6	
Week-8	11.3 ± 1.3	8.8 - 13.7	
Week-12	11.5 ± 1.5	9.1 - 14.2	
Differences between times (negative values indicate reduction)			
Times	**Mean ± SE**	**95% CI**	**#< 0.001***
Basal-Week-4	-1.3 ± 0.2	-1.8 - -0.9	#< 0.001*
Basal-Week-8	-1.6 ± 0.3	-2.2 - -1.0	#< 0.001*
Basal-Week-12	-1.4 ± 0.2	-1.9 - -0.9	#< 0.001*

Table 3: Hemoglobin changes in group A.

Group (B) showed non-significant SE except 2 cases stopped treatment due to decompensation "Ascites development".

Regarding dose modification of ribavirin in group A, in "week-4" 81.1% continued their treatment while 18.9% had dose modification. In "week 8" 78.4% continued their treatment while 21.6% had dose modification. No cases of treatment stoppage were reported (Table 4).

Time	Decision	%
Week-4	Continue	81.1
	Reduce	18.9
Week-8	Continue	78.4
	Reduce	21.6
Any time	Continue	64.9
	One reduction	29.7
	Two reductions	5.4

Table 4: Ribavirin dose modifications.

Cost effectiveness analysis reviewed that the whole cost of treatment process in group A 434,520 EGP (each patient cost 3,621 EGP) to get 111 SVR, so each one SVR case cost 3,914 EGP.

In Group B the whole cost was 598,290 EGP (each patient cost 5,390 EGP) to get 104 SVR, so each one SVR case cost 5,753 EGP. Group A relatively cost 50% of group B expenses, in addition to shorter duration, lower visits numbers (Table 5).

	Group A (N = 120)	Group B (N = 111)
Total expenses	434,520 EGP	598,290 EGP
Expense per patient	3,621 EGP	5,390 EGP
Single Sustained virological response cost	3,914 EGP	5,753 EGP

Table 5: Cost effectiveness comparison between two groups.

EGP: Egyptian Pound.

Discussion

The main goal of treatment of HCV patients is to eliminate the viremia, minimize the progression of the liver disease and to decrease the incidence of hepatocellular carcinoma [7]. Before the introduction of the DAAs the treatment regimen was confined to the interferon with high rates of treatment failure and relapse and a lot of documented side effects [10]. With the introduction of the DAAs in 2011, higher SVR rates, good tolerability with minimal side effects could be achieved [11,12].

Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor approved by the US Food and Drug Administration on 2013, for the treatment of chronic HCV infection [13]. Since its introduction to the market; Sofosbuvir has become a cornerstone in nearly all treatment regimens for HCV till now [7].

Daclatasvir is a protein 5A (NS5A) inhibitor. According to EASL guidelines; Treatment of Genotype 4 HCV could be achieved using Sofosbuvir 400 mg/Daclatasvir 60 mg regimen for 12 weeks in treatment naive patients, and for 24 weeks for treatment experienced or 12 weeks with addition of daily weight-based ribavirin [13].

Co-administration of these drugs has pan genotypic anti-HCV effect through inhibition of both NS5A, NS5B proteins. The combination of Daclatasvir and Sofosbuvir has been associated with high rates of sustained virological response and a favorable side-effect profile [7].

Side effects of ribavirin are mostly related to anemia and its mostly dose dependent which is mostly decreased by prescribing a fixed dose of 800 mg daily for that reason the initial dose of ribavirin in group A will be initiated by 600 mg to minimize the side effects although we can titrate the dose up to 1000 - 1200 mg/day [14]. No other clinical or significant laboratory changes was reported. Group (B) also didn't showed a significant clinical or laboratory changes, except the 2 pre mentioned cases who stopped treatment due to decompensation.

Our study has showed that using SOF/DCV/RBV for 12 weeks is much better in nearly all pillars of cost effectiveness than using SOF/DCV for 24 weeks. Group A showed nearly half financial expenses of group B (3914 EGP versus 5753 EGP) In addition to lower the financial burden that occur due to transportations and work absenteeism during visits.

Although group B showed slightly higher SVR rates 93.7%; it was not clinically significant. Group A showed no SE except anemia which was clinically significant, but all cases were controlled by only dose modification without the need to stop the drugs or adding any hematopoietic drugs.

So, if we weight the advantages against disadvantages of both groups, we will find that group B did a slightly higher SVR, with Lower SE but with double financial burden. On the other hand group A has a shorter course, half price, easily controllable SEs.

Conclusion

Treatment regimen of SOF/DCV/RBV for 12 weeks is much cost effective than SOF/DCV for 24 weeks, especially in low income countries. Unless there is a contraindication to ribavirin administration.

Disclosure

Authors didn't receive any financial support, and they have no conflict of interest to declare.

Bibliography

1. Papatheodoridis G and Hatzakis A. "Public health issues of hepatitis C virus infection". *Best Practice and Research Clinical Gastroenterology* 26.4 (2012): 371-380.

2. Ringehan M., *et al*. "Viral Hepatitis and Liver Cancer". *Philosophical transactions of the Royal Society of London. Series B, Biological Sciences* 372.1732 (2017): 20160274.

3. Gomaa A., *et al*. "Hepatitis C Infection in Egypt: Prevalence, Impact and Management Strategies". *Hepatic Medicine: Evidence and Research* 9 (2017): 17-25.

4. Kandeel A., *et al*. "The prevalence of hepatitis C virus infection in Egypt 2015: implications for future policy on prevention and treatment". *Liver International* 37.1 (2017): 45-53.

5. Jiménez-Pérez M., *et al*. "Treatment of chronic hepatitis C with direct-acting antivirals: The role of resistance". *World Journal of Gastroenterology* 22.29 (2016): 6573-6581.

6. Zarębska-Michaluk D., *et al*. "Predictors of sustained virological response in patients with hepatitis C virus genotype 3 infection". *Clinical and Experimental Hepatology* 2.3 (2016): 117-124.

7. "EASL Recommendations on Treatment of Hepatitis C 2016". *Journal of Hepatology* 66.1 (2017): 153-194.

8. National committee for control of viral hepatitis.

9. El-Akel W., *et al*. "National treatment programme of hepatitis C in Egypt: hepatitis C virus model of care". *Journal of Viral Hepatitis* 24.4 (2017): 262-267.

10. Hasan F., *et al*. "Peginterferon Alfa-2b Plus Ribavirin for the Treatment of Chronic Hepatitis C Genotype 4". *American Journal of Gastroenterology* 99.9 (2004): 1733-1737.

11. Jacobson IM., *et al*. "Telaprevir for previously untreated chronic hepatitis C virus infection". *New England Journal of Medicine* 364.25 (2011): 2405-2416.

12. Poordad F., *et al*. "Boceprevir for untreated chronic HCV genotype 1 infection". *New England Journal Medicine* 364.13 (2011): 1195-1206.

13. "AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus". *Hepatology* 62.3 (2015): 932-954.

14. Sulkowski MS., *et al*. "Anemia during treatment with peg interferon alfa-2b/ribavirin and boceprevir: Analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial". *Hepatology* 57.3 (2013): 974-984.

Volume 1 Issue 2 October 2018