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Safety and Efficacy of a Sofosbuvir Based Combination in Treatment of Egyptian Patients with Chronic Hepatitis C Genotype 4

Abdel-Hameed I.M. Ebid[1], Mohammed Ahmed Mobarez[1], Ramadan Ahmed Ramadan[2]
1. Department of Pharmacy Practice, Faculty of Pharmacy, Helwan University. Cairo, Egypt.
2.Internal Medicine, Hepatology Department, Ahmed Maher teaching Hospital, Cairo, Egypt.

ABSTRACT

Little is known about the safety and predictors of response of interferon (IFN), ribavirin (RBV), and sofosbuvir (SOF) combination in real-world settings. Hepatitis C virus (HCV) treatment decisions must depend on Real-world effectiveness data rather than clinical trails data., thus, the aim of this study is to comprehensively evaluate the safety and efficacy of this treatment in routine medical practice. A total of 105 treatment naïve patients with CHC genotype 4 with mean age 49 ± 7.26 years old of whom 62 were males and 43 were females, were treated with INF, RBV, and SOF for 12 weeks. Patients were monitored for safety and efficacy during the treatment and 12-week follow up periods. Seventy (66.67%) patients achieved a sustained virological response (SVR). The rate of SVR varied significantly by age, baseline fibrosis stage, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Scr), and hemoglobin (Hb). Most adverse effects were mild to moderate in severity and were well tolerated. The overall continuance rate without dose reduction was 80.95%. one patient discontinued treatment, due to neutropenia,. Hematologic toxicity included anemia with a frequency 19.05%. The efficacy of IFN/RBV/SOF combination for treatment of Egyptian CHC patients with genotype 4 in real-world setting was less than that reported in clinical trials.

Keywords: HCV, Interferon, Ribavirin, Sofosbuvir, SVR.

*Corresponding Author Email: mobarezmohamed@yahoo.com
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INTRODUCTION

Hepatitis C virus (HCV) is a hepatotropic RNA virus with a propensity to cause chronic infection, causing a global burden of chronic hepatitis C (CHC), cirrhosis and hepatocellular carcinoma (HCC). CHC infection is the major cause of chronic liver cirrhosis, hepatocellular carcinoma and the leading indication for liver transplantation[1]. Nearly 123 million people in world are currently infected with the HCV.[2] In Egypt, the prevalence is more worse. The national prevalence rate of HCV antibody positivity estimated at 14.7% of the country's population[3, 4]. with an estimated 91% of infections are caused by genotype 4[5] .So, Egypt has the highest HCV antibody positivity in the world[6, 7] .Today, HCV infection and its complications are one of the biggest public health challenges in Egypt[8] .

Anti-viral therapy for chronic hepatitis C virus (HCV) infection is rapidly evolving. Information derived from HCV anti-viral clinical trials may be limited in applicability to clinical practice where variations in patient characteristics, care coordination and management cannot be as tightly controlled. Differences between real-world HCV care outcomes and clinical trials often become apparent once these medications are prescribed to a broader population[9-12]. Understanding the effectiveness of anti-viral regimens in real-world settings is essential to provide practical information to better inform HCV treatment decisions.

While sustained virological response (SVR) rates reported in clinical trials with sofosbuvir (SOF)-based regimens represent a substantial improvement over previous interferon (IFN) and ribavirin (RBV) combination regimens, gaps in the evidence remain. For example, the US Food and Drug Administration (FDA) approval of SOF for genotype 4 treatment-experienced patients was based on modeling on small number of genotype 4, as this group was not evaluated in large clinical trials.[13]

Determination of factors affecting response, adverse effects and outcomes of HCV anti-viral regimens is a priority for the Egyptian health care policy decision makers. With the rapid uptake of SOF-based regimens across healthcare settings, and the underrepresentation of important populations in clinical trials, we examined the real-world outcomes of the diverse HCV-infected Egyptian population receiving this regimen. Our aim was to assess the effectiveness of IFN/RBV/SOF combination regimen in genotype 4 HCV-infected Egyptian patients treated in routine medical practice.

MATERIALS AND METHOD

Patient Selection:

Adult Egyptian patients with previously untreated CHC that had started treatment at Ahmed Maher Teaching Hospital in the period from August 1st, 2015 to September 1st, 2015 were screened and entered the study if they: were aged 18-65 years old, had at least one elevated serum alanine aminotransferase (ALT) level more than twice the upper limit of normal during the 6 months before treatment, had positive serum anti-HCV antibodies, had a detectable HCV-RNA on testing with polymerase chain reaction (PCR), and agreed to sign an informed consent to participate in the study.

Patients were excluded from the study if they: don't meet the above mentioned inclusion criteria, had other causes of chronic liver disease (hepatitis B infection, autoimmune hepatitis, metabolic liver disease such as hemochromatosis or chronic alcoholism), were co-infected with human immunodeficiency virus (HIV), were pregnant or breast feeding females, had ischemic heart disease (IHD), had severe neurologic or psychological conditions, had hematologic conditions such as white blood cell (WBC) count < 3.5×10^6 /mm^3, absolute Neutrophilic count (ANC) < 1500 /mm^3, hemoglobin (Hg) < 12 gm/dl, or platelet (PLT) count < 100,000 /mm^3, or had autoimmune disease, hemolytic anemia, or poorly controlled diabetes mellitus (HbA_{1c} > 8.5%).

Patients included or excluded from the study according to Ahmed Maher Teaching Hospital protocol.

Treatment:

Selected patients were assigned to receive 400 mg of oral Sofosbuvir (Sovaldi®;Gilead Sciences, Inc.) ,160 µgm of 20-kDa linear pegylated INF alpha-2a (Reiferon Retard®; Rhein-Minapharm Inc.) once a week for 12-weeks subcutaneous and oral ribavirin (Ribavirin®; Minapharm Inc.) 1000 mg/day for patients weighing < 75 kg and 1200 mg/day for patients weighing > 75 kg. INF dose was reduced to 120 µgm/week if: ANC < 750 /mm3, PLT < 50,000 /mm3, Hg < 8.5 g/dl. INF administration was temporarily suspended if ANC < 500 /mm3 and was permanently discontinued if ANC < 350 /mm3 or PLT < 25,000 /mm3. RBV dose was reduced to 600 mg/day if Hg < 10 gm/dl.

Monitoring:

Patients were carefully monitored every week by physical examination with stress on treatment induced adverse effects together with laboratory parameters evaluations that included: complete blood picture (CBC), aspartate aminotransferase (AST), ALT, total bilirubin, international

normalized ratio (INR), serum creatinine, thyroid stimulating hormone (TSH) level, and alpha fetoprotein (AFP) level. Serum HCV-RNA levels were measured at 4th, 12nd, and 24th weeks of treatment.

Virologic Assessment and Definition of Virologic Response:

HCV-RNA was quantified by Amplicor Monitor Assay; Roch Molecular Systems. The specimen requirement for HCV-RNA by PCR is one EDTA Serum needs to be separated from cells within 6 hours of collection and refrigerated or frozen to avoid degradation of viral RNA. A DNA copy of viral RNA is synthesized by reverse transcription. This DNA molecule is amplified millions of times by PCR. The lower limit of detection for the assay was 0.6 KIU/ml.

The end of treatment response (ETR) as undetectable HCV-RNA at the end of the 12-week course of treatment; and sustained virological response (SVR) as undetectable HCV-RNA 12 weeks after finishing treatment. Patients had a detectable HCV RNA at any time after the ETR, had no viral load testing after the ETR and a detectable HCV RNA on their last HCV viral load test while on treatment or died were considered non-responders and had to discontinue treatment according to hospital protocol. This was also done with patients who showed reappearance of HCV-RNA while on treatment (breakthrough response). Relapse is defined as reappearance of HCV-RNA after finishing the course of treatment. Anti-viral efficacy was evaluated for all study patients using intention-to-treat analysis (ITT analysis).

Statistical Analysis:

Results are presented as means ± standard deviations (SD) for continuous variables, median and range for non-normally distributed variables, and as frequencies and percentages for categorical data.

Analysis of normality was performed using the Kolmogorov-Smirnov test. Categorical data and proportions were analyzed using the $\chi 2$ test or the Fisher's exact test, as required. Student's t test was used to compare the means of the 2 groups with normal distributions, and the Mann-Whitney U test was used to compare variables with non-normal distributions. All tests were 2-tailed. P-values <0.05 were considered statistically significant. Analysis was conducted using SPSS version 22.

RESULTS AND DISCUSSION

Baseline Characteristics:

The study was performed from August 2015 to February 2016 at Ahmed Maher Teaching Hospital. A total of 105 treatment naïve Egyptian CHC patients were studied of whom 62

(59.04%) were males and 43 (40.95%) were females. The mean age for studied patients was 49 ± 7.26 years old. Table 1 summarizes the baseline demographic and clinical data for the studied population.

Table 1: Patients' Baseline Demographic and Clinical Features.

Characteristic	Value
Number of patients	105
Age* (years)	49 ± 7.26
Sex (male/female)	62 / 43
Body Weight* (kg)	73.97 ± 11.39
Albumin* (g/dl)	4.08 ± 0.40
ALT* (IU/L)	65.09 ± 55.24
AST* (IU/L)	61.14 ± 35.10
ALP* (IU/L)	110.84 ± 43.66
AFP** (ng/ml)	5.1 / 0.5 – 35
Total Bilirubin* (mg/dl)	0.82 ± 0.46
Serum Creatinine* (mg/dl)	0.80 ± 0.19
WBC* (×1000/mm^3)	5.99 ± 1.52
Hemoglobin* (g/dl)	13.98 ± 1.71
PLT* (×1000/mm^3)	182.33 ± 53.05
TSH* (mIU/L)	1.54 ± 0.65
Fasting blood glucose* (mg/dl)	99.33 ± 27.59
HbA_{1c} *, *** (%)	9.23 ± 2.13
Viral load**, **** (KIU/ml)	231 / 1.46 – 14574
METAVIR fibrosis score (0-2/3-4)	46 / 59

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **ALP:** alkaline phosphatase; **AFP:** alpha-feto protein; **WBC:** white blood cells; **PLT:** platelets; **TSH:** thyroid stimulating hormone; **HbA_{1c}:** Glycated hemoglobin.

* mean ± SD, ** median / range, *** for patients with fasting blood glucose > 126 mg/dl (n=21). **** 1 KIU/ml = 900 copies/ml

Adverse Events (AEs):

All patients had at least one AE during treatment. Most treatment-related AEs were considered mild or moderate in severity and were consistent with flu-like symptoms such as fever, headache, and fatigue. All AEs reported are summarized in Table 2.

Clinical Laboratory Evaluation:

Most changes in laboratory values were mild or moderate, as classified by World Health Organization (WHO) criteria. Grade 4 (<500/mm^3) neutropenia occurred in one (0.95%) discontinued treatment at week 8 (ANC 345/mm^3) and not achieved an SVR.

The magnitude of reductions in hemoglobin concentration from baseline was similar in all age groups. At nadir, the mean change from baseline was – 3.45 ± 1.91 g/dl. Anemia was managed

through dose reduction of RBV in 20 (19.05%) patients. Table 3 summarizes laboratory abnormalities encountered during treatment.

Dose Reduction / Treatment Discontinuation for AEs:

The overall continuance rate without dose reduction was 80.95% one patient discontinued treatment, because of febrile neutropenia. IFN or RBV dose reductions were required for 20 (19.05%) patients, usually because of anemia 20 (19.05%). Causes and frequency of dose reduction and treatment discontinuation and their effect on viral response are summarized in Table 4.

Virological Response:

Six (5.72%) patients were non-responders, where as 99 (94.28%) patients attained ETR of whom 29 (27.62%) had a relapse while 70 (66.67%) patients achieved SVR. Fig. 1 and Fig. 2 summarize viral responses in the studied patients.

Factors associated with SVR were assessed using variables in Table 1. Significant factors included: age, baseline viral load, baseline METAVIR fibrosis score, AST, ALT, Serum Creatinine, Hemoglobin. Table 5 summarizes the effect of studied patients' variables on SVR rate.

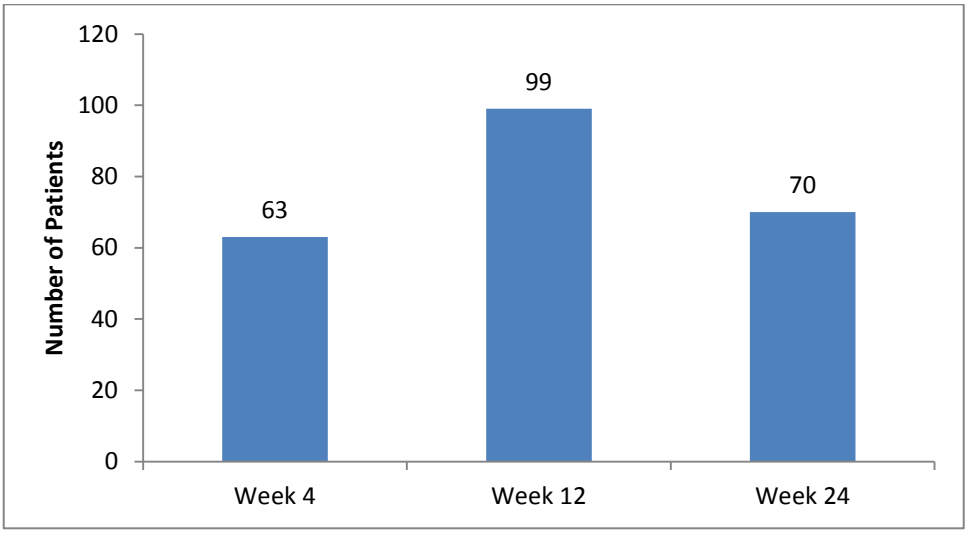

Figure 1: Number of patients with undetectable HCV-RNA by weeks of treatment.

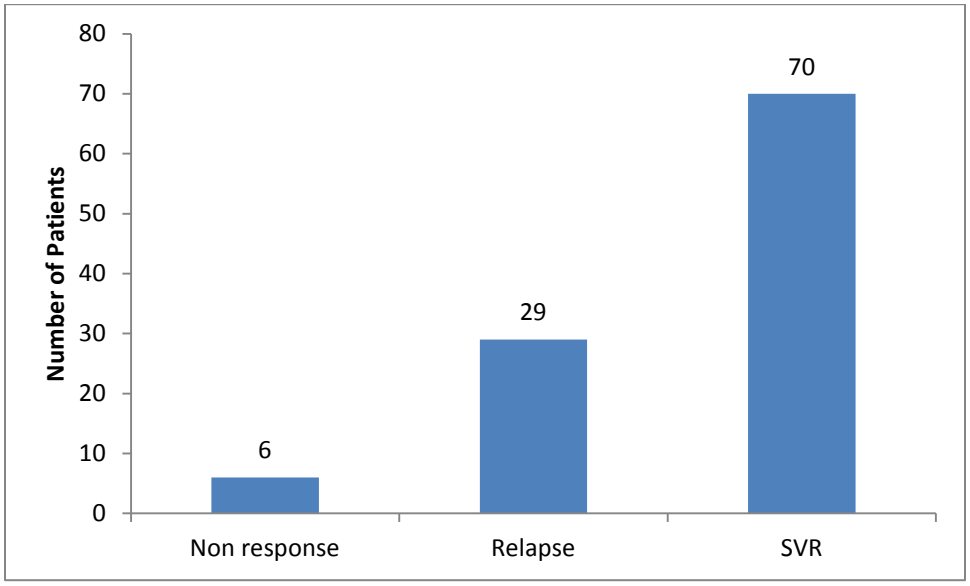

Figure 2: distribution of virological response among patient population

DISCUSSION

Egypt has possibly the highest HCV prevalence in the world; 10%–20% of the general population are infected and HCV is the major cause of HCC and chronic liver disease in the Egypt[14-18]. Improperly sterilized parenteral administration tools used in Parenteral antischistosomal treatment campaign that took place in the 1930s is the start and leading cause of the epidemic[3]. Although such treatment has discontinued since the late 1980s, the transmission of infection is still going in modern day Egypt[8]. Much of this transmission occurs through iatrogenic and interfamilial routes of transmission[19, 20]. Nevertheless, a significant number of CHC Egyptian patients have an unknown source of infection indicating that there is unknown methods of transmission[21]. That is why treatment is considered a corner stone in the control of hepatitis C epidemic in Egypt.

Real-world data about the safety and efficacy of IFN/RBV/SOF combination in HCV genotype 4 are limited. In the registration trial (NEUTRINO trial) by Lawitz *et al* [13]. only 28 treatment-naïve patients with HCV genotype 4 infection were enrolled. The SVR frequency among this subgroup was 96.4% which is obviously greater than our reported frequency of 66.67%, also our study largely differ from result of Wehmeyer, et al[22] which report that patients receving SOF/IFN/RBV achieve 100% SVR which reflects that data obtained from clinical trials are not always reproducible in real clinical settings.

The efficacy of IFN/RBV/SOF combination in our study patients is comparable to daclatasvir based therapy and simeprevir based therapy[23, 24].

The response to treatment of CHC with IFN/RBV/SOF combination varies considerably among different populations and viral genotypes. Studies that investigate the effect of patients' baseline variables on the frequency of SVR are limited. Our study demonstrates that SVR rate varies significantly with age, fibrosis stage, baseline viral load, AST, ALT, serum creatinine, and hemoglobin. Baseline serum total bilirubin and TSH had normal baseline value in almost all patients so, effect of both could not be determined.

The safety and tolerability issues reported in our study is similar to that reported by Wehmeyer, et al[22] that most common adverse events were fatigue, headache, and gastrointestinal symptoms. Other treatment related adverse events are summarized and stratified by age in (table 2). We report a 19.05% frequency of anemia (Hg < 10 gm/dl) lead to dose reduction of RBV but we notice that 70% of these patients achieved SVR and because anemia mainly due to RBV which illustrate that RBV has role in achieving high SVR (table 4). One case of treatment discontinuation due to neutropenia is reported in our study. On the other hand Wehmeyer, et al reported a 12.5% frequency of anemia, 12.5% for neutropenia, and Ribavirin dose reduction was necessary in (25%) of patients.

Table 2: Treatment related Adverse Events Stratified by Age

AE, n (%)	18–35 Y (n = 7)	36–50 Y (n = 52)	51–65 Y (n= 46)	All Patients (n = 105)
General constitutional symptoms				
Fever	6 (85.71%)	34 (65.38%)	29 (63.04%)	69 (65.71%)
Chills	7 (100%)	16 (30.77%)	19 (41.3%)	42 (40%)
Fatigue	7 (100%)	33 (48.84%)	47 (63.46%)	87 (82.86%)
Weight loss*	2 (28.57%)	8 (15.38%)	6 (13.04%)	16 (15.24%)
ISR	5 (71.43%)	6 (11.54%)	11 (23.91%)	22 (20.95%)
Gastrointestinal disorders				
Nausea	7 (100%)	3 (5.77%)	10 (21.74%)	20 (19.04%)
Vomiting	5 (71.43%)	7(13.46%)	8 (17.39%)	20 (19.04%)
Abdominal Pain	3 (42.86%)	6 (11.54%)	7 (15.22%)	16 (15.24%)
Anorexia	5 (71.43%)	14 (26.92%)	11 (23.91%)	30 (28.57%)
Respiratory tract disorders				
Breathlessness	3 (42.86%)	6 (11.54%)	5 (10.87%)	14 (13.33%)
Cough	5 (71.43%)	18 (34.62%)	15 (32.61%)	38 (36.19%)
Musculoskeletal disorders				
Arthralgia	5 (71.43%)	14 (26.92%)	20 (43.48%)	39 (37.14%)
Myalgia	4 (57.14%)	18 (34.62%)	20 (43.48%)	42 (40%)
Nervous system disorders				
Headache	7 (100%)	38 (73.08%)	35 (76.09%)	80 (76.19%)
Dizziness	3 (42.86%)	7 (13.46%)	5 (10.87%)	15 (14.23%)
Psychological Disorders				
Nervousness &	6 (85.71%)	14 (26.92%)	6 (13.04%)	26 (24.74%)

aggression				
Insomnia	7 (100%)	8 (15.38%)	11 (23.91%)	26(24.76%)
Anxiety	5 (71.43%)	3 (5.77%)	2 (4.35%)	10 (<10%)
Depression	5 (71.43%)	3 (5.77%)	5 (10.87%)	13 (12.38%)
Skin disorders				
Hair fall	4 (57.14%)	3 (5.77%)	10 (21.74%)	17(16.19%)
Pruritus	3 (42.86%)	2 (3.85%)	3 (6.52%)	8(<10%)

AE: adverse event; **Y:** years old; **ISR:** injection site reaction.

* > 5% from baseline.

Table 3: Treatment related Laboratory Abnormalities

Laboratory test	Nadir, mean ± SD	Change from baseline, mean ± SD
ANC, (/mm^3)	1900.08 ± 888.95	-3180.28 ± 1668.38
Hg, (g/dl)	9.75 ± 0.95	-3.45 ± 1.91
PLT, (×1000/mm^3)	117.22 ± 37.86	-69.44 ± 54.82

ANC: Absolute Neutrophilic Count; **Hg:** Hemoglobin; **PLT:** Platelets.

Table 4: Adverse Events Leading to Dose Reduction or Interruption.

Adverse Event	Frequency, n (%)	Management	SVR rate, n (%)
Anemia	20 (19.05%)	20 RBV dose reduction	14 (70)
		0 RBV & INF dose reduction	N/A
Neutropenia	1 (0.95)	1Treatment Discontinuation	0 (0)
		0 Suspended INF	N/A
		0 INF dose reduction	N/A

SVR: Sustained Virological Response; **INF:** Interferon; **RBV:** Ribavirin; **N/A:** Not Applicable.

Table 5: Difference in Baseline Variables Between Patients Who Achieved SVR and Those Who didn't.

Factor		Viral Response		*p*-value
		SVR	Non-SVR	
Age	18-35	2	0	0.015*
	36-50	37	20	
	51-65	31	15	
Sex	Male	42	20	0.779
	Female	28	15	
Baseline Viral Load*** (KIU/ml)	Very low**	2	3	0.009*
	Low**	23	4	
	Moderate**	33	20	
	High**	12	10	
METAVIR fibrosis	0-2	37	10	0.023*
	3-4	33	25	
Albumin (gm/dl)		4.09 ± 0.39	4.05 ± 0.43	0.381
AST (IU/L)		55.41±32.78	76.4 ± 39.64	0.009*
ALT (IU/L)		57.28 ± 41.94	98.48 ± 67.44	0.002*
ALP (IU/L)		114.57 ± 41.48	103.40 ± 47.47	0.218
Total bilirubin**** (mg/dl)		0.79 ± 0.42	0.86 ± 0.54	0.487

Serum creatinine**** (mg/dl)	0.84 ± 0.84	0.73 ± 0.13	0.003*
TSH**** (mIU/L)	1.98 ± 1.26	2.04 ± 1.13	0.837
WBC (/mm^3)	5988.50 ± 1492.49	6000.63 ± 1598.44	0.964
Hemoglobin (gm/dl)	14.25 ± 1.66	13.44± 1.69	0.022*
Platelets (/mm^3)	180385.7 ± 6018.36	186200 ± 65491.27	0.893
AFP*** (ng/ml)	6.076	6.4	0.482

SVR: sustained virological response; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; WBC: white blood cells; AFP: alpha feto protein.

* Statistically significant difference between SVR and non-SVR groups.

** Very low < 10 KIU/ml, low < 100 KIU/ml, moderate < 1000 KIU/ml, high > 1000 KIU/ml.

*** Results are reported as median and Mann-Whitney U test was used to detect significance.

**** Effect may be unclear because all patients had a normal baseline values.

CONCLUSION

The efficacy of IFN/RBV/SOF combination for treatment of Egyptian CHC patients with genotype 4 in real-world setting was less than that reported in clinical trials. Nevertheless, this combination is still in effective enough so that more researches and treatment combination needed to combat hepatitis C epidemic in Egypt at reasonable cost. The response to IFN/RBV/SOF combination in CHC Egyptian patients varies depending factors including: age, fibrosis stage, baseline viral load, AST, ALT, serum creatinine, and hemoglobin. Knowledge of these factors is crucial before treatment decisions for individualized patient case by case and to determine patients' priority treatment in case of scarce financial resources allocation especially in developing countries as in Egypt.

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