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Therapeutic outcome of 6198 interferon-naïve Egyptian patients with chronic hepatitis C: a real-life experience and lessons to be learned in DAAs' era

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SUMMARY. Antiviral therapy for HCV infection has been validated in randomized controlled clinical trials, but its value in the real world is less well studied. There is relatively little data on real-world responses to interferon-based therapies for patients with genotype 4 infection. We aimed to examine experience with large-scale access to antiviral therapy in chronic HCV in a real-life clinical setting in Egypt. Detailed pretreatment data of 6198 IFN-naïve chronic HCV patients who had received PEG-IFN/RBV therapy at Cairo-Fatemic Hospital, Egypt, between 2009 and 2012 were obtained from the HCV database. At week 12, 95.7% of patients had undetectable HCV RNA, and by week 24 and 48, breakthrough was 6% and 4%, respectively. However, 43.7% of patients discontinued treatment prematurely, and intent to treat end of treatment response was 44.6% (79.3% per protocol). Sustained response data were available from only 1281 patients and was 84.9%. Haematological abnormalities were comparable in patients who did or did not comply with therapy. This is the first real-world, large-scale experience of antiviral therapy in chronic HCV in Egypt. Suboptimal response in HCV predominantly genotype 4 was mainly driven by noncompliance as well as gaps in the healthcare system leading to treatment discontinuation. These results need to be considered in the era of all oral antiviral regimes.

Keywords: Egypt, HCV, real experience, treatment.

INTRODUCTION

Hepatitis C virus (HCV) is highly endemic in Egypt where nearly 9.8% of the population are chronically infected [1]. The majority (91%) of patients are infected with HCV genotype 4 (HCV4) [2].

Until the launch of all oral therapies for HCV, the recommended standard of care for HCV genotype 4 was a combination of pegylated interferon (PEG-INF) and ribavirin [3,4]. This combination has relatively high efficacy with SVR in patients with genotype 4 ranging from 42% to over 60% in randomized controlled trials (RCTs) [5].

Abbreviations: AFP, alfa-feto protein; ALT, alanine amino-transferase; AST, aspartate amino-transferase; BMI, body mass index; ETR, end of treatment response; EVR, early virological response; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; RCTs, randomized controlled trials; SVR, sustained virological response.

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Even with the emergence of the new oral antiviral drugs, Peg-INF/RBV will retain an important role in the context of large numbers of patients and limited resources in developing countries [6].

Despite its high efficacy in clinical trials, the effectiveness of Peg-INF and ribavirin therapy in community-based practice is unclear. Clinical trials typically evaluate carefully selected participants with few or no contraindications, and patients undergo closer monitoring than would be seen in most clinical settings [7–10].

It is, therefore, important to understand the 'real-world' treatment effectiveness, so we can identify gaps in the spectrum of care and thereby improve the effectiveness of therapy. With the release of newer, more efficacious therapies, addressing the effectiveness gaps in real-world clinical practice will be increasingly important [10–12].

In Egypt, the national programme for HCV treatment has provided a rich pool of data on real-world treatment outcomes. Here, we report one of the largest studies to-date examining HCV treatment effectiveness in a real-life high-volume clinical setting in a community-based practice in a resource limited setting.

PATIENTS AND METHODS

The study sample

This cross-sectional observational study involved a database of 6198 Egyptian, IFN-naïve chronic HCV patients who had received PEG-IFN/RBV therapy between 2009 and 2012 at Cairo-Fatemic Hospital, Egypt, one of the largest centres for treatment of viral hepatitis affiliated to the Minstry Of Health And Population (MOHP). Adult patients aged 18–60 years old who had serological, virological and histo-pathological evidence of HCV infection were referred from different geographical locations in Egypt and evaluated for the eligibility to receive combined pegylated interferon/ribavirin therapy.

Inclusion criteria for therapy were according to national guidelines, and interferon-naive Egyptian patients of both sexes chronically infected with HCV were enrolled if they fulfilled the following criteria:

- Adult without previous antiviral therapy, BMI ≤ 35, evidence of serological, virological and histological chronic HCV as evidenced by positive HCV antibodies (using a third-generation ELISA test) and detectable HCV RNA. HCV RNA was expressed in IU/ml and measured by COBAS® AmpliPrep/COBAS® TaqMan® HCV assay
- Serum transaminases (alanine aminotransferase (ALT) levels and (AST)) levels above the upper limit of normal (ULN) or at least ≥ F2 stage of fibrosis (Metavir score) on a liver biopsy in patients with normal enzymes.
- Haematological profile: white blood cell (WBC) > 4.000/mm³, neutrophil count >2.000/mm³, platelets >100.000/mm³
- Biochemical liver profile: direct bilirubin 0.3 mg/dl or within 20% of ULN, PT < 2 s above ULN, albumin > 3.5 gm/dl
- Normal kidney function tests and controlled blood sugar in patients with diabetes.
- TSH within normal range and ANA titre < 1:40.

Patients with decompensated liver disease, co-infected patients with HBV (positive HBsAg), patients with hepatocellular carcinoma, patients with severe psychiatric disease and patients with serious co-morbid conditions were excluded.

Enrolment assessment

A standardized enrolment questionnaire was completed by the patients' physicians. Each patient was subjected to a detailed medical history and clinical assessment after signing written informed consent.

Laboratory procedures

Blood tests performed at enrolment covered aspects of general health, for example complete blood picture with special emphasis on haemoglobin level, total and differential leucocyte count and platelet count. Other blood tests performed included parameters of the HCV virus infection (serum HCV RNA level), HCV-related liver disease (levels of liver enzymes; AST, ALT), markers of hepatic synthetic function (serum albumin and INR) and HBsAg. Other laboratory tests included TSH, ANA, antischistosomal antibodies. All laboratories performed regular quality controls to ensure the validity of their results.

Liver biopsy was performed under ultrasonography guidance after checking the adequacy of the patients' coagulation profile. The Metavir scoring method was used, and histological activity index (HAI) was determined [13]. Only liver biopsy samples with at least 10 mm long or had six portal tracts were examined to allow for adequate interpretation. Patients with inadequate liver biopsy samples were sent for re-biopsy.

Table 1 Baseline demographic, laboratory and histopathological data of the whole studied group (6198 patients)

	Mean and standard deviation
Demographic	
Gender	Number and percent
Male	5044 (81.4%)
Female	1154 (18.6%)
Age	41.57 ± 9.93
BMI (Kg/cm^2)	28.07 ± 4.26
Laboratory	
Total bili (mg/dl)	0.90 ± 2.09
AST (mIU/ml)	57 ± 40.66
ALT (mIU/ml)	64 ± 49.80
Albumin (g/dl)	4.3 ± 1.60
AFP (ng/ml)	6.27 ± 11.46
Glucose (mg/dl)	99 ± 29
Creatinine (mg/dl)	0.91 ± 0.37
WBCs ($\times 10^3$)	6.48 ± 1.87
HB (g/dl)	14.1 ± 1.54
Platelets ($\times 10^3$)	215.32 ± 71.538
TSH	1.62 ± 2.35
Viral load ($\times 10^3$)	1588.281 ± 1.5117
Histopathology*	
Histological Activity (A)	
A0	7 (0.2%)
A1	2365 (60.5%)
A2	1230 (31.4%)
A3	310 (7.9%)
Stage of Fibrosis (F)	
F1	782 (20%)
F2	2399 (61.3%)
F3	476 (12.2%)
F4	255 (6.5%)

*Available histopathology data of 3912 patients only.

Data collection

Ethical approval for data collection was obtained from Ministry of Health and Population ethics committee. Data were obtained from HCV patients' medical records. Data collected included demographic, laboratory, ultrasonographic data and liver biopsy results.

Statistical analysis

The descriptive statistics were provided with mean ± standard deviation (SD) or median for nonparametric data. The χ^2 test and student *t*-test were employed for analysis of qualitative or quantitative variables, respectively. Pearson correlation was done to correlate continuous variables. In all tests, *P* values were significant if less than 0.05.

RESULTS

This cohort included 6198 Egyptian chronic HCV patients. Baseline demographic, laboratory and histopathological data are shown in Table 1.

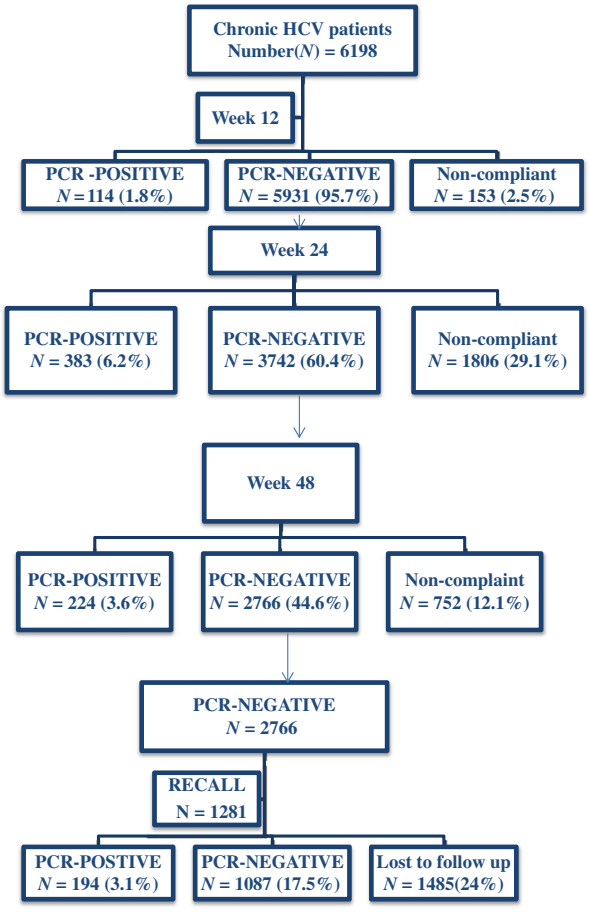

Fig. 1 Therapeutic outcome of 6198 chronic HCV patients in a real-life clinical setting in Egypt.

Figure 1 and Table 2 show the response to therapy. At week 12, the early virological response (EVR) was very high – 95.7%. At week 24 and 48, breakthrough was 6% and 4%, respectively, but 43.7% (n = 2711) of patients discontinued treatment. The end of treatment response (ETR) was 44.6% (n = 2766/6198), and SVR was 17.5% (n = 1087/6198) according to an intention to treat analysis whereas, ETR and SVR almost doubled (79.3%, 31.2%, n = 2766/3487, n = 1087/3487, respectively) in a per protocol analysis. However, treatment failure was dominated by nonattendance, and in the 1281 patients who reattended for a post-treatment assessment, the response rate was 84.9% with relapse rate of 15.1%.

There was no statistically significant difference between the compliant and noncompliant patients regarding the demographic characteristics apart from BMI, total bilirubin, serum glucose and AFP (*P* value 0.044, 0.004 and 0.001, respectively) (Table 3).

As haematological abnormalities are considered the most common side effects that lead to either dose modification or discontinuation, we examined haematological parameters in patients who discontinued therapy and those who did not. However, in this study, haematological abnormalities were comparable in patients who did or did not discontinue treatment (Table 4).

To try and investigate the main causes for noncompliance, particularly between 12 and 24 weeks of treatment (period of maximum drop-out), a telephone call random survey on 100 patients was performed. Although this may not be representative of the total study population, it provided some preliminary information about possible reasons for noncompliance of patients (Table 5).

DISCUSSION

In Egypt, the national programme for HCV treatment has provided a rich pool of data which have led to the conduction of large population-based studies. This is one of the largest studies examining HCV treatment effectiveness.

Despite the high efficacy of pegylated interferon and ribavirin in clinical trials, the effectiveness of antiviral therapy in community-based practices is quite different where the well-designed individualized therapy adopted in RCT is not always applied [10].

It is important to understand the current state of treatment effectiveness, so we can identify the gaps in the spectrum of care that may cause a decline in effectiveness.

Based on previous clinical trials, the SVR for genotype 4 was 42–60%; however, in our study this was not the case. In our study of 6198 patients, the overall effectiveness of HCV treatment was 17.5% for the entire study population, declining from 95.7% at w12 to 60% at w24 with ETR of 44.6%. However, SVR was not properly assessed for the

Table 2 Therapeutic Outcome of 6198 chronic HCV patients in a real-life clinical setting

	Number	Percent	Cumulative percent
Noncompliant at w12	153	2.5	2.5
Noncompliant at w24	1806	29.1	31.6
Noncompliant at w48	752	12.1	43.7
Lost to follow up at w72	1485	24	67.7
SVR	1087	17.5	85.2
Nonresponder	915	14.8	100.0
Total	6198	100	

Table 3 Baseline demographic characteristics and laboratory values of both compliant and noncompliant patients

Variable	Compliant (n = 3487) Mean ± SD	Noncompliant(n = 2711) Mean ± SD	P-value
Age	41.75 ± 9.70	41.32 ± 10.24	0.117
Gender			
Male	2832 (81.2%)	2212 (81.6%)	0.665
Female	656 (18.8%)	498 (18.4%)	
BMI (kg/cm^2)	28.33 ± 4.26	27.727 ± 4.25	0.000*
Total bilirubin(mg/dl)	0.850 ± 1.36	0.975 ± 2.80	0.044*
Indirect bilirubin(mg/dl)	0.62 ± 2.12	0.67 ± 1.67	0.405
Albumin (g/dl)	4.25 ± 1.15	4.27 ± 2.07	0.59
AST (mIU/ml)	55.97 ± 40.40	58.11 ± 41.01	0.055
ALT (mIU/ml)	63.81 ± 49.61	64.34 ± 50.07	0.701
Haemoglobin (gm/dl)	14.11 ± 1.52	14.15 ± 1.57	0.358
WBC ($\times 10^3$)	6.50 ± 1.86	6.44 ± 1.89	0.244
ANC ($\times 10^3$)	3.45 ± 1.29	3.41 ± 1.31	0.384
Platelets ($\times 10^3$)	216.26 ± 66.54	214.03 ± 77.92	0.263
Glucose (mg/dl)	98.47 ± 27.51	100.76 ± 30.82	0.004*
Creatinine (mg/dl)	0.917 ± 0.35	0.907 ± 0.38	0.322
Serum AFP (ng/ml)	5.77 ± 10.93	6.98 ± 12.12	0.000*
TSH	1.58 ± 1.12	1.68 ± 3.38	0.147

*Values are statistically significant.

entire group due to high numbers of both noncompliant and lost to follow up individuals. SVR data from patients (1281) who attended appropriately were 84.9%.

There was no statistically significant difference between the compliant and noncompliant patients regarding the demographic characteristics, and we are, therefore, unable to predict which patients are most likely to default.

As haematological abnormalities are considered the most common side effects that lead to either dose modification or discontinuation, we examined haematological parameters in patients who continued and those who did not continue treatment. However, in this study, haematological abnormalities were comparable and thus patients' noncompliance remains unexplained.

The total percentage of noncompliant patients was 43.7% (n = 2711). The period expected to show the highest dropout of patients is the first 12 weeks of treatment (being the period during where most of side effects are experienced), but in our study, this was period had the lowest rate of discontinuations (153 patients – 2.5%) perhaps because in the early stages patients were highly motivated.

Most of the noncompliant patients (n = 1806, 29.2%) defaulted between weeks 12 and 24. On trying to identify the main causes for noncompliance a phone call survey on 100 patients was conducted and this identified three main factors: firstly, gaps in the healthcare system due to limited treatment centres leading to overcrowding, long queues and waiting hours, travelling long distances either to get treatment for follow-up appointments. In addition, lack of proper communication skills of medical staff and lack of call back systems once a patient missed his scheduled visit were noted. Secondly, factors related to the patients' compliance were common with the long duration of treatment and side effects being cited as personal reasons for noncompliance. Lastly, defects in the database (10%) that either used single contact point for patients (for example, a single cell phone number which proved to be nonfunctional) or using an incorrect home address.

Table 4 Comparison of on-treatment haematological abnormalities between compliant and noncompliant groups

Parameter	Group	*P*-value within group	*P*-value between both groups
HB drop*	Compliant	0.004	0.267
	Noncompliant	0.808	
WBCs drop†	Compliant	0.302	0.957
	Noncompliant	0.887	
Platelets drop‡	Compliant	0.000	0.046
	Noncompliant	0.002	

*A significant HB drop in both groups (compliant and noncompliant); however, there is no significant difference in drop pattern.
†TLC does not show significant difference in both groups during follow-up.
‡A significant drop of platelets in both groups with significant difference in drop pattern between the two groups.

Our study shows the efficacy of PEG-INF and ribavirin treatment in a national sample of patients was low, and failure to achieve SVR was driven by several factors. The most important obstacles in reducing the effectiveness of HCV antiviral treatment were noncompliance (particularly with the prolonged duration of treatment) that could be solved by orientation sessions for patients before starting treatment, establishing call back systems with well-trained nurses to contact the patient early if an appointment is missed and continued medical education with particular emphasis on the value of communication skills to encourage, support and deal with side effects experienced by patients while on treatment. In addition, applying the new shorter antiviral therapies may promote compliance. More frequent data auditing, more regular supervision of data entry and more efficient computer backup systems will help to minimize the loss of data.

In conclusion, this is the first large-scale study of experience with antiviral therapy in chronic HCV patients on a nationwide scale in Egypt – a country known for its heavy burden of HCV infection and limited resources. Suboptimal response in HCV genotype 4 was mainly driven by noncompliance rather than side effects as well as gaps in the healthcare system leading to patients refraining from using healthcare services. Further efforts are needed to address the gaps in our healthcare systems which will improve the effectiveness of HCV treatment and, ultimately, reduce the burden of liver disease in Egypt.

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CONFLICTS OF INTERESTS

Regarding this manuscript, all authors disclose no conflicts apart from Professor Gamal Esmat who disclose the following: (i) Advisory Committee Board Member: Merk, Gilead and Bristol-Myers; (ii) Speaking and Teaching activities: Roche, Bristol-Myers, Merck and Glaxo; (iii) Grants and research support: Gilead, Roche, Merck, Glaxo, Janssen, Abbvie and Pharco.

Table 5 Reasons of noncompliance of patients while on treatment

Reasons	Number
Overcrowding, long queues and long waiting hours	25
Patient declining treatment by themselves without obvious medical cause	17
Refusal to continue for long duration	14
Travelling long distances (particularly, poor rural areas) to receive treatment or for follow-up laboratories	13
Inability to tolerate treatment	8
Considering EVR as a full response	7
Inadequate communications skills of medical staff	6
Others*	10

*Other causes observed during making phone calls, the only contact number in patients' medical records is not a working number (missing data: database did not include two contact numbers including landlines or clear home address).

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