The Efficacy of a *Hansenula*-Derived 20 kDa Pegylated Interferon Alpha-2a in the Treatment of Genotype 4 Chronic Hepatitis C

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Pending the emergence and approval of an effective interferon-free regimen, pegylated interferon will remain an integral part of the treatment of genotype 4 hepatitis C virus (HCV). A new 20 kDa pegylated interferon has been developed in a cost-saving fungal-based system and is commercialized in Egypt at a quarter to a third of the price of conventional pegylated interferon. We hereby test the efficacy and safety of this novel cost-saving interferon. One hundred ninety-three consecutive treatment-naïve patients with genotype 4 HCV were treated using the following regimen: subcutaneous 20 kDa pegylated interferon 160 µg once weekly plus oral ribavirin 1,000 or 1,200 mg daily (based on body weight <75 kg or ≥75 kg, respectively) for 48 weeks. A sustained virological response (SVR) of 51% was achieved. Interim responses included rapid virological response (RVR): 54%, early virological response (EVR): 78% (complete EVR: 71%, partial EVR: 7%), and end of treatment response: 63%. The most common adverse events were flu-like symptoms, dyspepsia, anorexia, and pruritus. Treatment-related serious adverse events were encountered in only 2 patients (1%). Discontinuation of treatment due to adverse events occurred in only 13 patients (7%). Multiple logistic regression analyses revealed the following factors as predictors of SVR: RVR ($P < 0.001$), alpha-fetoprotein < upper limit of normal (ULN) ($P = 0.007$), and early biochemical response (alanine aminotransferase < ULN at week 12, $P = 0.018$). *Hansenula*-derived 20 kDa pegylated interferon alpha-2a is an effective and safe treatment for genotype 4 chronic HCV. These results highlight the presence of a less costly treatment for chronic HCV, pending the emergence of an effective inexpensive interferon-free regimen. A direct comparison with 40 kDa interferon remains essential to adequately compare the efficacy and safety.

Introduction

CHRONIC HEPATITIS C has a significant prevalence worldwide with a remarkably high prevalence in Egypt reaching 15% (Egyptian Ministry of Health 2007). Genotype 4 is the overtly prevalent genotype in Egypt affecting more than 95% of patients (Egyptian Ministry of Health 2007). Pegylated interferon has been the suboptimal “gold standard” for the treatment of hepatitis C virus (HCV) during the past 2 decades with sustained virological response (SVR) rates ranging from 40% to 60% when combined with ribavirin (Kamal and Nasser 2008). Apart from the mediocre response, the other main disadvantage of interferon is its high cost forming a huge burden on the economy of developing countries, such as Egypt. Novel direct acting antivirals (DAAs) have shown very promising results, but until these results are confirmed and until the substantial cost of

these agents is reduced to be feasible for use in developing countries, pegylated interferon will remain the mainstay of treatment for several more years (Pol and others 2012; Lawitz and others 2013a, 2013b).

A novel linear 20 kDa pegylated interferon alpha-2a derived from the yeast *Hansenula polymorpha* (Reiferon Retard, Minapharm Pharmaceuticals, Cairo, Egypt) has been approved for the treatment of HCV in Egypt despite the scarcity of clinical studies supporting its efficacy (Taha and others 2010). This novel interferon has an attractive advantage of being almost 4-fold less costly than standard 40 kDa pegylated interferon. The low cost of production is attributed to very short fermentation times and a significantly reduced number of downstream steps, resulting in a higher purity, with no forms of oxidized interferon being detected (Gelissen 2002). This is an independent investigator-driven study to assess the efficacy and safety of *Hansenula*-derived

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20 kDa pegylated interferon alpha-2a in the treatment of genotype 4 chronic HCV.

Patients and Methods

Patients

This is a retrospective study assessing all patients treated by 20 kDa pegylated interferon alpha-2a at the Hepatology Department of the National Railway Hospital Center, Cairo, Egypt. During the period between December 2010 and January 2012, consecutive treatment-naïve chronic HCV patients presenting to our department were treated by 20 kDa pegylated interferon and ribavirin. Patients were considered eligible for the treatment under the following criteria: detectable HCV-RNA by PCR, alanine aminotransferase (ALT) elevation above upper limit of normal (ULN), and/or liver biopsy showing fibrosis score $>F1$ on the Metavir grading system and age between 18 and 65 years. Exclusion criteria included: inadequate hematologic indices (hemoglobin <12.5 g/dL in men or <12 g/dL in women, neutrophils $<1,500/\text{mm}^3$, platelets $<75,000/\text{mm}^3$), decompensated liver disease (bilirubin >2.5 g/dL, albumin <3.5 g/dL, INR >1.3 , or clinical evidence of decompensation), body mass index (BMI) >35 kg/m, HBV or HIV coinfection, significant medical comorbidities, drug abuse, alcohol consumption >20 g/day, uncontrolled autoimmune or psychiatric illness, and pregnancy and lactation.

The treatment regimen included subcutaneous 20 kDa pegylated interferon 160 μg once weekly (Reiferon retard; Minapharm, Cairo, Egypt) plus oral ribavirin (Ribavirin; Minapharm) 1,000 or 1,200 mg daily (based on body weight <75 kg or ≥ 75 kg, respectively) for 48 weeks. Patients were evaluated clinically together with laboratory testing every 2 weeks during the first 4 weeks and every 4 weeks thereafter and every 12 weeks after the end of the treatment. HCV-RNA was recorded at baseline and at week 4, 12, 24, 48 and 6 months after the end of the treatment (Cobas Ampliprep/Cobas Taqman, lower limit of detection 15 IU/mL; Roche Molecular Systems, Pleasanton, CA).

All patients gave a written informed consent, and the study was approved by the local ethics committee and was performed in accordance to the Declaration of Helsinki. The study was fully funded by the National Railway Hospital Center (a nonprofit governmental organization) with no support from the industry.

Efficacy assessment

Our primary outcome of efficacy was the rate of SVR as defined by an undetectable serum HCV-RNA 24 weeks after the end of the treatment. Secondary outcome parameters included rates of rapid virological response (RVR), complete early virological response (CEVR), and end of treatment response (ETR) defined as serum HCV RNA below the limits of detection at 4 and 12 weeks of combination treatment and at the end of the treatment, respectively. Partial early virological response (PEVR) was defined as detectable serum HCV RNA with a more than 2 log drop from baseline to 12 weeks. Early biochemical response (as defined by an ALT $\leq$ ULN) was also evaluated at 12 weeks. Patients who had less than 2 log drop in serum HCV-RNA at 12 weeks of combination therapy or detectable serum HCV RNA at 24 weeks of combination therapy were considered as treatment failures, and the treatment was discontinued.

Safety assessment

Safety assessment was performed throughout the treatment and follow-up, including clinical examination and laboratory assessment. Adverse events, dose reductions, and withdrawals due to intolerance were recorded and documented. Adverse events were graded as mild, moderate, severe, or life-threatening according to the US Division of Microbiology and Infectious Diseases (DMID 2007) adult toxicity tables. Significant neutropenia was considered when the absolute neutrophil count was below $1,000/\text{mm}^3$, significant anemia when hemoglobin level was below 10 g/dL, and significant thrombocytopenia when platelets were below $100,000/\text{mm}^3$. Epoetin beta (Recormon; Roche, Basel, Switzerland) was the initial management of choice for hemoglobin levels between 8.5 and 10 g/dL, failure of epoetin was then managed by stepwise reduction in ribavirin dose by 200 mg decrements down to 600 mg/day and discontinued if hemoglobin decreased below 8.5 g/dL. Filgrastim (Neupogen; Roche) was the initial management of choice for neutrophil counts between 750 and $1,000/\text{mm}^3$. The dose of pegylated interferon was reduced to 80 μg weekly for neutrophil counts between 500 and $750/\text{mm}^3$ or platelet counts below $50,000/\text{mm}^3$ and discontinued for neutrophil counts below $500/\text{mm}^3$ and platelet counts below $30,000/\text{mm}^3$.

Statistical methods

The chi-square test or the Fisher's exact test for small sample size was used to compare between the subgroups. To study the independent effect of the possible prognostic factors of SVR, a stepwise logistic regression analysis was performed (Dawson and Trap 2001). Univariate logistic regressions were used to confirm the importance of previously identified prognostic factors. To assess the independence of these, a backward elimination procedure was then undertaken using the factors that were significant in the univariate analyses. All *P* values are 2-sided. *P* values <0.05 were considered significant. Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 17.

Results

Patient demographics

During the period between December 2010 and April 2012, 193 patients were treated using 20 kDa pegylated interferon in addition to ribavirin. Demographic and baseline data are demonstrated in Table 1. Thirteen patients (7%) did not complete the treatment due to adverse events and 7 patients (4%) were lost during the follow-up after completing the treatment. All patients receiving at least 1 dose of interferon were included in the efficacy and safety analyses.

Virological responses

An SVR of 51% was achieved. Interim responses included RVR: 54%, EVR: 78% (CEVR: 71%, PEVR: 7%), and ETR: 63% (Figs. 1 and 2). The relapse rate after achieving an end-of-treatment response was 22%. Early biochemical response (defined as ALT $\leq$ ULN at 12 weeks) was observed in 67% of patients.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

Sex M/F (% male)	186/7 (96)
Age	46 (21–63)
BMI	27.7 (18.5–35)
DM	31 (16)
ALT, U/L	65 (14–335)
HCV-RNA, IU/L $\times 10^5$	3.9 (0.02–76.3)
High viral load ($>400,000$ IU/L)	96 (50)
Advanced fibrosis (F3, F4)	66 (34)
Significant NAFLD ^a	32 (18)

^aDefined as steatosis $>33\%$ on liver biopsy (moderate and severe steatosis).

Categorical parameters are numbers (percentages); continuous parameters are median (range).

ALT, alanine aminotransferase; BMI, body mass index; DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; HCV, hepatitis C virus.

Predictors of response

To assess possible prognostic factors and their impact on SVR, the following factors were analyzed first separately by univariate analysis: age (>40 vs. ≤ 40 years), sex, BMI (<25 vs. ≥ 25 and <30 vs. ≥ 30), diabetes, positive schistosomiasis serology, ALT and AST levels ($<2 \times \text{ULN}$ vs. $\geq 2 \times \text{ULN}$), alkaline phosphatase level ($\leq \text{ULN}$ vs. $> \text{ULN}$), platelets ($<150,000$ vs. $\geq 150,000$), viral load ($<400,000$ U/L vs. $\geq 400,000$ U/L), Metavir fibrosis score ($\leq \text{F2}$ vs. $> \text{F2}$), steatosis (no and mild steatosis vs. moderate and severe steatosis), alpha-fetoprotein ($\leq \text{ULN}$ vs. $> \text{ULN}$), RVR, and early biochemical response. Factors showing a significant association with an SVR were alpha-fetoprotein $< \text{ULN}$ ($P < 0.001$), early fibrosis (Metavir F score ≤ 2 , $P = 0.002$), early biochemical response ($P < 0.001$), and RVR ($P < 0.001$). Significant factors were entered in a multiple logistic regression where the following factors maintained their significance: RVR, alpha-fetoprotein, and early biochemical response (Table 2).

Safety

The most common adverse events were flu-like symptoms (fever, fatigue, headache, myalgias, arthralgias, headache),

FIG. 1. Virological response rates. RVR, rapid virological response; EVR, early virological response; ETR, end of treatment response; SVR, sustained virological response. *Seven patients missed doing the PCR at week 4. †Seven patients were lost during the follow-up after the end of treatment.

FIG. 2. Sustained virological response rates according to the fibrosis stage. Patients with early fibrosis had significantly better sustained virological response than patients with advanced fibrosis (59.3% vs. 34.9%, $P = 0.002$).

dyspepsia, anorexia, and pruritus (Table 3). Treatment-related serious adverse events were encountered in only 2 patients (1%), both suffered severe anemia necessitating blood transfusion. Neutropenia appeared during the first 2 weeks in all patients suffering neutropenia and stabilized thereafter. Significant anemia and thrombocytopenia occurred during the first 8 weeks, except for 2 patients where significant anemia occurred at week 12. The dose of interferon was reduced due to neutropenia in 10 patients (5%). Other causes of interferon dose reduction included thrombocytopenia in 4 patients (2%) and facial palsy in 1 patient (0.5%). Dose reduction of ribavirin occurred in 11 patients (6%), all due to anemia. Discontinuation of treatment due to adverse events occurred in 13 patients (7%). The main causes of treatment discontinuation were neutropenia (3 patients), anemia (3 patients), and in 1 patient each: thrombocytopenia, retinopathy, glomerulonephritis, cancer prostate, ischemic heart disease, and facial palsy. Neutrophil counts returned spontaneously to baseline levels within 2 weeks after cessation of therapy, whereas hemoglobin levels and platelet counts returned spontaneously to baseline after 4 to 6 weeks. Facial palsy was partially reversible while retinopathy and glomerulonephritis did not regress spontaneously after cessation of therapy. The patient with ischemic heart disease did not have significant anemia and suffered angina and ischemic ECG changes at week 33 of treatment, whereas Hgb level was 11.2 g/dL. All other reported adverse events resolved spontaneously after the end of treatment. Dose reductions had no significant impact on SVR: patients having interferon dose reductions had an SVR of 47%

TABLE 2. PREDICTORS OF RESPONSE ON MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

	Odds ratio	95% CI	P value
RVR	6.77	3.23–14.8	<0.001
AFP ($\leq \text{ULN}$)	3.8	1.45–9.99	0.007
Early biochemical response ($\leq \text{ULN}$ 12 weeks)	2.74	1.19–6.35	0.018

RVR, rapid virological response; AFP, alpha-fetoprotein; ULN, upper limit of normal.

TABLE 3. INCIDENCE OF ADVERSE EVENTS, DOSE MODIFICATION, AND TREATMENT DISCONTINUATION

	Number (%)
Serious adverse events	
Any	3 (2) ^a
Treatment-related	2 (1)
Discontinuation of treatment due to adverse events	13 (7)
Dose adjustments/growth factors	
Dose reduction due to any adverse event	26 (14)
Dose reduction of interferon	15 (8)
Dose reduction of ribavirin	11 (6)
Dose reduction due to anemia	11 (6)
Dose reduction due to neutropenia	10 (5)
Use of epoetin	48 (25)
Use of filgrastim	48 (25)
Adverse event ^b	
Fever	130 (67)
Fatigue	130 (67)
Musculoskeletal (myalgia, arthralgia)	78 (40)
Headache	60 (31)
Dyspepsia	60 (31)
Pruritus	55 (28)
Anorexia	48 (24)
Constipation	17 (9)
Depression	14 (7)
Cough	12 (6)
Diarrhea	12 (6)
Insomnia	10 (5)
Rash	11 (5)
Hematologic adverse events	
Anemia (Hgb < 10 g/dL)	64 (33)
Neutropenia (ANC < 1,000/mm ³)	60 (31)
Thrombocytopenia (< 100,000/mm ³)	35 (18)

^aOne patient developed cancer prostate, 2 suffered severe anemia.

^bAdverse events occurring in ≥5% of patients.
ANC, absolute neutrophil count.

(7/15), patients having ribavirin dose reductions had an SVR of 50% (5/10). Treatment discontinuation had a significant impact on SVR as only 4 of 13 patients (31%) achieved an SVR. Epoetin and filgrastim were used at least once in 48 patients (25%) each.

Discussion

Chronic HCV forms an immense financial and social burden especially in developing countries. Genotype 4 is arguably the most difficult to treat with response rates in the range of 50% with the current standard of care, including pegylated interferon and ribavirin (Kamal and Nasser 2008). This standard of care is therefore far from optimal and also comes with a great financial burden. At the time of conduction of this study, a standard course of 48 injections of 40 kDa pegylated interferon alpha-2a cost ~11,200\$, a cost that is not affordable by the vast majority of patients in Egypt. When considering the prevalence of HCV reaching about 15% (ie, 12.75 million Egyptian patients), it becomes obvious that the economy of a developing country could not withstand such a burden. Over the past 2 decades, there has been a relentless quest to develop a more effective and less costly alternative to pegylated

interferon. Regarding a more effective agent, boceprevir and telaprevir have shown good results yet only when added to interferon and not in genotype 4 HCV (Jacobson and others 2011; Poordad and others 2011). More recent DAAs such as daclatasvir and sofosbuvir seem to be the eventual answer; however, so far the published studies have mainly addressed only genotypes 1–3 (Pol and others 2012; Lawitz and others 2013a, 2013b). The recent NEUTRINO study included patients with genotype 4 treated with sofosbuvir, an SVR rate of 96% was achieved, but it has to be noted though that the regimen consisted of sofosbuvir in addition to pegylated interferon and ribavirin (Lawitz and others 2013b). Another major setback for novel DAAs is that they are even more costly than interferon, ~5-folds more expensive than 40 kDa pegylated interferon. So, until a novel agent proves effective as a single drug in genotype 4 patients and the price falls to at least the price of interferon, we will have to depend on pegylated interferon for several more years, at least in developing countries with a high prevalence of genotype 4, such as Egypt.

In 2007, a novel pegylated 20 kDa *Hansenula*-derived interferon alpha-2a was developed and approved for the treatment of HCV in Egypt. To our knowledge, apart from an abstract presented at a conference meeting (Esmat and Abdel-Fattah 2009), only one published study has directly addressed the efficacy of this novel interferon (Taha and others 2010). In 107 patients, an SVR of 60% was achieved (Taha and others 2010). A recent randomized trial not intended at assessing the efficacy of 20 kDa interferon included an arm of 50 patients who received the 20 kDa interferon together with ribavirin; the SVR was 50% in this arm (Shehab and others 2014). Our study included 193 patients and an SVR of 51% was achieved. These results suggest that the 20 kDa interferon may compare favorably to previous reports of conventional 40 kDa pegylated interferon alpha-2a (Khuroo and others 2004; Kamal and Nasser 2008). A meta-analysis in 2004 assessing the effect of 40 kDa pegylated interferon in genotype 4 reported an SVR rate of 55% (Khuroo and others 2004). More recent studies including genotype 4 patients reported SVR rates between 43% and 61% (Asselah and others 2012; De Nicola and others 2012; Abdo and others 2013; Antaki and others 2013; Derbala and others 2013; El Raziky and others 2013; Urquijo and others 2013; Youssef and others 2013). The variability of reported results adds to the importance of a head-to-head trial that is essential to confirm the similar efficacy of the 2 interferons. The implications of our results are substantial; our study proves that the less costly 20 kDa pegylated interferon is effective and safe in the treatment of genotype 4 HCV. At the time the study was initiated, the price of 48 injections of 20 kDa pegylated interferon was 3,200\$ compared to 11,200\$ for conventional 40 kDa pegylated interferon, almost a quarter. Recently, the presence of the novel interferon has led to a considerable drop in the prices of 40 kDa interferon in Egypt, yet it remains significantly more expensive. The presence of such a cheaper yet effective alternative will immensely aid the national efforts to eradicate HCV. Interim responses also compared similarly, yet our RVR rate was unexpectedly high (54%) in comparison to previous reports of only 16%–45% with 40 kDa interferon (Kamal and others 2007; Ferenci and others 2008). We postulated that this might be due to the strict measures we took to ensure compliance in the early

weeks of treatment, but this argument, however, fails to explain why the high RVR did not translate to higher ETR and SVR rates. There have been anecdotal reports of a higher relapse rate with the novel interferon; however, our relapse rate was 22%, within the range reported for 40 kDa interferon (16%–32%).

The good response rates obtained despite treating a relatively difficult-to-treat group of patients. A large portion of our patients had advanced fibrosis (34%), had a high viral load (50%), were of older age (median 46 years), were overweight (median BMI 27.7), had significant steatosis (18%), and were diabetic (16%). This group of patients therefore constituted a real test for the efficacy of the 20 kDa pegylated interferon; the efficacy does not seem to be affected more than conventional 40 kDa pegylated interferon by the usual predictors of poor response. To curb this enthusiasm, we have to acknowledge that a clear comparison with 40 kDa interferon can only be done through a randomized controlled trial.

This new interferon also seems to have similar predictors of response as the 40 kDa interferon. As expected, the RVR was the strongest predictor of an SVR. Advanced fibrosis also seemed to be a predictor of poor response; however, it failed to maintain in the multiple logistic regression. Similar to our finding, an elevated alpha-fetoprotein has been recently reported to be a strong predictor of poor response with 40 kDa interferon (Khairy and others 2012; Zayed and others 2013). An early biochemical response has not previously been well-acknowledged as a clear predictor of response. A recent study has assessed early biochemical response at 4 weeks and revealed a strong association with an SVR (Kim and others 2012). We believe that a normal ALT level at 12 weeks especially in patients who started out with an elevated ALT level should be considered as a strong predictor of response and should—together with RVR, alpha-feto protein, and fibrosis levels—be used to formulate a prediction of the response and guide treatment decisions made by the physician and the patient.

Regarding the safety profile of the 20 kDa interferon, it seems to be generally similar to that of conventional 40 kDa interferon, with flu-like symptoms, dyspepsia, anorexia, and pruritus being the most frequent symptoms. Noteworthy is the low rate of discontinuation of treatment due to adverse events (7%). We do however relate this to our treatment protocol rather than the nature of the interferon. Our treatment protocol involved the liberal use of hematopoietic growth factors aiming at avoiding dose reductions/discontinuation as much as possible. This policy led not only to the frequent use of growth factors but also to a low rate of dose reduction/discontinuation: treatment discontinuation due to adverse events was only 7% compared to 10%–14% in the largest published trials (Manns and others 2001; Fried and others 2002; McHutchison and others 2009). Similarly, our rate of dose modification was 14% compared to 14%–42% reported in the literature (Manns and others 2001; Fried and others 2002; McHutchison and others 2009). Anemia (Hgb < 10 g/dL) was encountered in 33% of our patients compared to 23%–30% in the literature (Manns and others 2001; Fried and others 2002; McHutchison and others 2009). Epoetin was used in 25% of patients, as our rate of anemia is similar to that reported in the literature; we believe that the frequent use of epoetin was not attributable to the frequency of anemia but rather to the set treatment

protocol advocating the liberal use of growth factors before attempting dose reductions. Neutropenia was encountered in 32% of our patients, a seemingly high rate compared to 18%–27% in the literature (Manns and others 2001; Fried and others 2002; McHutchison and others 2009). However, we believe that this is partly attributable to the definition of neutropenia we used (< 1,000/mm³), whereas many studies use 750/mm³ as a cut-off for the definition of neutropenia. This explanation is supported by the fact that significant neutropenia necessitating the administration of filgrastim occurred in only 25% and dose reduction in only 5% of patients. The incidence of depression seems to be low in this cohort of patients (7%), yet it has to be noted that cultural factors may play a role in the reporting of depression. In our country, many patients still consider psychiatric problems as taboo, many have profound fears of taking antidepressants or sedatives, and many also fear that by reporting they have depression might prevent them from continuing the treatment. Despite the investigators persistent efforts to alleviate such fears, we still believe that this symptom is largely underreported by our patients. This observation is supported by the low rates of depression reported in other studies conducted in our country using 40 kDa interferon (Kamal and others 2005; Shehab and others 2014).

Our study has some noteworthy limitations. There were a very low number of females in our studied group (4%); this finding is similar to several studies conducted in Egypt (Esmat and others 2003; Rossignol and others 2009). This could be explained by the low educational and economic levels of the studied population where it is still difficult for many women to seek medical care, traveling to medical centers is still difficult for many women, and unfortunately, many myths exist linking HCV treatment with lifelong sterility in females. In our study, the preferential selection of males was amplified by the fact that our hospital supplied treatment for workers at the national railway system, the majority of whom are men. Strictly speaking, this means that our results apply mainly to men and interpretation for female patients should be done with caution. Second, our study was conducted on Egyptian patients with genotype 4, and therefore, the reproducibility of results among other populations remains questionable. Third, our study did not assess IL28 genotypes that are now known to impose a large impact on virological response rates (Jiménez-Sousa and others 2013). It would have also been very interesting to assess the pharmacokinetics of this novel interferon to compare with 40 kDa interferon, unfortunately, this was beyond the financial limits of our study.

In conclusion, 20 kDa pegylated interferon alpha-2a is effective and safe in the treatment of genotype 4 chronic HCV when combined with ribavirin. A randomized controlled trial comparing it with 40 kDa pegylated interferon is warranted to confirm our observations suggesting similar efficacy and safety. These results highlight the presence of a less costly treatment for chronic HCV, pending the emergence of an effective inexpensive interferon-free regimen.

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Author Disclosure Statement

No competing financial interests exist.

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