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Therapy of Hepatitis C — Back to the Future

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A book on hepatitis C would read like a marriage of an Orson Welles mystery and a Shakespearean play — awash in enigma, tragedy, despair, resilience, redemption, and triumph. It is only fitting that treatment of hepatitis C virus (HCV) infection stands at center stage of such a book. After the initial introduction of interferon alfa as the mainstay of therapy, the field stalled for more than 10 years. Although the introduction of ribavirin combination therapy and pegylated inter-ferons had increased response rates, the real breakthrough came with the development of direct-acting antiviral agents (DAAs).[1] The first generation of DAAs in combination with peginterferon and ribavirin showed improved response rates, but they were accompanied by worsening side effects that have precluded a great majority of patients from benefiting from therapy.

In a previous article in the *Journal*, we reviewed the current and future therapies for HCV infection and commented on the rapidly shifting therapeutic landscape.[1] We speculated that highly effective interferon-free regimens would be available and should revolutionize the treatment of HCV infection in the near future. Now, just 1 year after that review, we would have to say that the future is here.

The results of several phase 3 studies of inter-feron-free combination regimens of DAAs reported in the *Journal* now[2–4] and recently[5–9] (Table 1) unequivocally show the superiority of two such regimens over the standard-of-care treatment (a combination of peginterferon, ribavirin, and a protease inhibitor) for HCV genotype 1 infection. A previous editorial in the *Journal* highlighted the significantly improved response rates (rates of sustained virologic response of 93% to 99%) with a coformulated regimen of sofosbuvir (a nucleotide NS5B inhibitor) and ledipasvir (an NS5A inhibitor) among patients with HCV geno-type 1 infection, as compared with the rates with the previously approved interferon-based single-DAA combination therapy.[13]

Other studies reported in the *Journal* show similarly high response rates with a different combination of DAAs among patients with HCV genotype 1 infection.[2,3,8,9] This regimen includes three DAAs — ABT-450 (an NS3/4A inhibitor) coadministered with ritonavir (ABT-450/r), om bitasvir (an NS5A inhibitor), and dasabuvir (a nonnucleoside NS5B inhibitor) — with or without ribavirin. These studies evaluated the efficacy and safety of this regimen in patients who either were previously untreated or were previously treated with

peginterferon and ribavirin but without a sustained virologic response. In addition, safety and efficacy in patients with compensated cirrhosis were examined specifically in one study.[3] Like the studies of sofosbuvir and ledipasvir, these studies could use historical controls (treatment responses in previous phase 3 studies with the regimen of peginterferon, ribavirin, and a protease inhibitor) for comparison because of the anticipated wide difference in therapeutic margins between the old and new treatments.

In both studies involving patients without cirrhosis who were previously untreated or previously treated, the sustained-virologic-response rates were all about 96%,[8,9] findings that suggest that patients with a previous nonresponse to peginterferon and ribavirin are not particularly difficult to treat with this regimen. Patients with cirrhosis did not have quite as robust a response to this regimen, though the response rate was still more than 90%.[3] The study involving patients with cirrhosis also evaluated a treatment duration of either 12 weeks or 24 weeks and showed a modestly higher response rate in the 24-week group overall (96%, vs. 92% in the 12-week group), and secondary subgroup analyses suggest a greater response to the 24-week regimen, as compared with the 12-week regimen in patients with genotype 1a infection who had had a prior null response to peginterferon and ribavirin (93% vs. 80%).[3]

Several factors, such as racial or ethnic back ground, *IL28B* genotype, and baseline HCV RNA level, have been shown to influence treatment response to interferon-based therapy.[14] As in the studies of sofosbuvir and ledipasvir,[5–7] these factors do not play a prominent role in determining treatment response in these newer studies.[2,3] Probably because these factors are specifically linked to the actions of interferon in the treatment of HCV infection, they do not appear to affect the response rates of the more potent DAA-containing regimens. The only factor that was modestly associated with treatment response in the trials of combination regimens of DAAs was body-mass index in one study.[8] HCV geno-type 1a infection has been shown previously to respond less well to DAA-based therapy than genotype 1b infection,[15,16] but in these recent studies, HCV subgenotype did not seem to matter, other than in patients with cirrhosis. In one study, patients with genotype 1a infection seemed to benefit from the addition of ribavirin, whereas no significant difference was observed in patients with genotype 1b infection.[2]

The concept of response-guided therapy was introduced previously to tailor treatment duration on the basis of virologic response during treatment.[16,17] In the era of potent DAA combination therapies, the decline in serum viral levels was rapid and dramatic: by week 4 of treatment, 99% of patients had nonquantifiable HCV RNA in the blood. Therefore, response-guided therapy is no longer necessary with these interferon-free DAA-based regimens. All patients could probably be treated with a single duration of therapy, which will certainly simplify and facilitate monitoring during treatment.

An interferon-free regimen has also been developed for the treatment of HCV genotype 2 or 3 infection. In two trials reported in the *Journal* last year,[11,12] 12 weeks of treatment with sofosbuvir and ribavirin resulted in response rates of more than 90% among previously untreated patients with genotype 2 infection but only about 60% among previously untreated patients with genotype 3 infection. The authors of one of the studies also examined the

response rate with the same regimen among patients who did not have a response to prior treatment with peginterferon and ribavirin and found lower sustained-viro-logic-response rates (86% among patients with genotype 2 infection and 30% among patients with genotype 3 infection) than observed among previously untreated patients.[12] In the same study, extending the treatment duration to 16 weeks resulted in a doubling of the sustained-virologic-response rate over the 12-week regimen (from 30% to 62%) among patients with geno-type 3 infection.[12]

As reported in the *Journal*,[4] a follow-up study extended the treatment duration of patients with genotype 3 infection to 24 weeks and included both previously untreated patients and previously treated patients (with a nonresponse to peginterferon and ribavirin). Among previously untreated patients with or without cirrhosis, the longer duration regimen resulted in a response rate of more than 90%. However, among previously treated patients with cirrhosis, the response rate was significantly lower (62%). A close examination of the data suggests that relapse appeared to be the major reason for the nonresponse; among previously treated patients, extending therapy reduced the relapse rate from 66% with the 12-week duration to 20% with the 24-week duration.

Drug resistance against these DAAs is common in preclinical studies and with single-drug regimens in early clinical trials. Mathematical modeling has been applied to predict how many of these drugs are needed to minimize the drug-resistance problem.[18] Practically, the number of drugs needed in a treatment regimen depends on their anti-HCV potency and the genetic barrier to the development of resistant mutations. In the case of sofosbuvir and ledipasvir, a two-drug combination is sufficient; in the other regimen, a three-drug combination appears to be necessary to achieve high response rates without selecting for resistant mutants. For the small number of patients who did not have a sustained virologic response, sequence analysis of the prevailing viral strains at the time of relapse showed the presence of previously described mutations that are resistant to each of these drugs, with the exception of sofosbuvir. Sofosbuvir seems to have a high genetic barrier to resistance, which probably explains its notable efficacy in DAA combination regimens.

The side effects associated with interferon-based therapy have prevented many patients from undergoing treatment and are a major reason for treatment failure. Perhaps the more important achievement of these interferon-free regimens is the lower rate and severity of side effects associated with treatment. The duration of treatment is shorter, and although constitutional symptoms of fatigue, headache, pruritus, and nonspecific gastrointestinal symptoms are common, most patients do not rate them as severe. With ribavirin-containing regimens, anemia is a common but manageable problem. Elevated bilirubin levels are often observed and can be attributed to inhibition of the bilirubin transporter by one of the drugs in addition to ribavirin-associated hemolysis. Serious adverse events, although uncommon (affecting <5% of study participants), were reported. Some of the events could be related to the treatment regimens. One death was reported in the trial involving patients with compensated cirrhosis who received the regimen containing ABT-450/r, ombitasvir, dasabuvir, and ribavirin, although it is unclear whether this event was related to the treatment. Further monitoring will be necessary.

At this juncture, we are certainly not ready to close the book on the treatment of HCV infection. The regimens have been tested predominantly in middle-aged, white men without cirrhosis. More-difficult-to-treat patients, such as those with cirrhosis, human immunodeficiency virus and HCV coinfection, or renal failure, remain a challenge. It is also not clear whether these regimens will be effective in those infected with HCV genotypes 4, 5, and 6, which are common in many parts of the world. Finally, the cost of treatment, which was highlighted in a recent editorial in the *Journal*,[13] will continue to be a deterrent for population-wide applications of these highly effective regimens. This dilemma is not only a topic of ongoing debate in the more developed countries, such as the United States and western European countries, but it is also a truly global public health problem of enormous impact — the majority of people with HCV infection live in lower-income, resource-constrained regions of the world. As pointed out in our previous review article and a recent Perspective article in the *Journal*,[19] the challenge will indeed continue to be how we can leverage modern medical advances, such as the treatment of HCV infection, to benefit those who are most in need.

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Table 1.

Phase 3 Trials of Interferon-free Regimens for the Treatment of HCV Infection.*

Trial Name and Study Group†	Study Design	Status with Regard to Previous Treatment	No. of Patients	Sustained Virologic Response at Post-Treatment Wk 12		
				Overall	Genotype 1a *percent*	Genotype 1b
HCV genotype 1						
ION-1[5]	Randomized, open-label study; historical control	Untreated				
LDV-SOF, 12 wk			214	99	98	100
LDV-SOF + RBV, 12 wk			217	97	97	99
LDV-SOF, 24 wk			217	98	98	97
LDV-SOF + RBV, 24 wk			217	99	99	100
ION-2[6]	Randomized, open-label study; historical control	Treated				
LDV-SOF, 12 wk			109	94	95	87
LDV-SOF + RBV, 12 wk			111	96	95	100
LDV-SOF, 24 wk			109	99	99	100
LDV-SOF + RBV, 24 wk			111	99	99	100
ION-3[7]	Randomized, open-label study; historical control	Untreated				
LDV-SOF, 8 wk			215	94	93	98
LDV-SOF + RBV, 8 wk			216	93	92	95
LDV-SOF, 12 wk			216	95	95	98
SAPPHIRE-I[8]	Randomized, placebo-controlled study; historical control	Untreated				
AOD regimen + RBV, 12 wk			473	96	95	98
Placebo			158			
SAPPHIRE-II[9]	Randomized, placebo-controlled study; historical control	Treated				
AOD regimen + RBV, 12 wk			297	96	96	97
Placebo			97			
PEARL-III[2]	Open-label study; historical control	Untreated				
AOD regimen + RBV, 12 wk			210			100
AOD regimen, 12 wk			209			99
PEARL-IV[2]	Open-label study; historical control	Untreated				

Trial Name and Study Group[†]	Study Design	Status with Regard to Previous Treatment	No. of Patients	Sustained Virologic Response at Post-Treatment Wk 12		
				Overall	Genotype 1a *percent*	Genotype 1b
AOD regimen + RBV, 12 wk			100		97	
AOD regimen, 12 wk			205		90	
TURQUOISE-II[3][≠]	Open-label study; historical control	Untreated and treated				
AOD regimen + RBV, 12 wk			208	92	89	99
AOD regimen + RBV, 24 wk			172	96	94	100
HALLMARK DUAL[10]	Randomized, controlled study (previously untreated patients); open-label study (other patients)	Untreated and treated				
DCV + ASV, 24 wk			205[§]			90
Placebo, 12 wk			102[§]			
DCV + ASV, 24 wk			205[¶]			82
DCV + ASV, 24 wk			235[//]			82
				Overall	Genotype 2	Genotype 3
HCV genotypes 2 and 3						
FISSION[11]	Randomized, active-control study	Untreated				
SOF-RBV, 12 wk			256	67	97	56
PEG-RBV, 24 wk			243	67		
POSITRON[12]	Randomized, placebo-controlled study	Untreated				
SOF-RBV, 12 wk			207	78	93	61
Placebo			71	0		
FUSION[12]	Randomized, active-control study	Treated				
SOF-RBV, 12 wk			103	50	86	30
SOF-RBV, 16 wk			98	73	94	62
VALENCE[4]	Randomized, placebo-controlled study initially; switched to open-label study	Untreated and treated				
SOF-RBV, 12 wk			84	85	93	27
SOF-RBV, 24 wk			250			85

[*] HCV denotes hepatitis C virus.

[†] Coformulated ledipasvir (LDV)–sofosbuvir (SOF) was administered as a once-daily dose of 90 mg of LDV and 400 mg of SOF, with or without 1000 to 1200 mg of ribavirin (RBV) daily. Coformulated ABT-450 with ritonavir (ABT-450/r)–ombitasvir and dasabuvir (AOD regimen) was administered as a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir as well as 250 mg of dasabuvir twice daily, with or without 1000 to 1200 mg of RBV daily. Daclatasvir (DCV, an NS5A inhibitor) and asunaprevir (ASV, an NS3/4A inhibitor) were administered as 60 mg of DCV once

daily and 100 mg of ASV twice daily. SOF–RBV was administered as 400 mg of SOF once daily and 1000 to 1200 mg of RBV daily. Peginterferon (PEG)–RBV was administered as 180 μg of subcutaneous PEG once weekly and 800 mg of oral RBV daily.

‡All patients in this study had compensated cirrhosis.

§These patients were previously untreated.

¶These patients had a prior null or partial response to PEG–RBV.

//These patients were considered “intolerant to or ineligible for” PEG–RBV.