Maximizing Opportunities and Avoiding Mistakes in Triple Therapy for Hepatitis C Virus

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CLINICAL LIVER

Recently developed drugs and innovative strategies for the treatment of chronic infection with genotype 1 hepatitis C virus (HCV) have become the standard of care. The protease inhibitors telaprevir (Incivek) and boceprevir (Victrelis) are the first direct-acting antiviral (DAA) agents approved, and many more are being developed. These drugs substantially increased rates of sustained virologic response in treatment-naïve and -experienced patients, in conjunction with peginterferon and ribavirin (triple therapy), in phase 3 trials. The efficacy of triple therapy depends on appropriate selection of patients, although the population of patients that receive triple therapy could be expanded as the risk/benefit ratio improves. Attention to details that reflect the standard of care, such as appropriate dosing, anticipation of adverse effects, and strict adherence to stopping rules, will insure the success of these drugs and lead the way for new combination therapies.

Keywords: Hepatitis C; Boceprevir; Telaprevir; Safety; Triple Therapy.

In 2011, great advances were made in the treatment of chronic infection with genotype 1 hepatitis C virus (HCV). Gastroenterologists and hepatologists now treat these patients with the immunomodulator peginterferon (PEG-IFN) and ribavirin (RBV), combined with direct-acting antiviral (DAA) agents. Telaprevir (Incivek; Vertex Pharmaceuticals, Inc, Cambridge, MA) and boceprevir (Victrelis; Merck & Co, Inc, Whitehouse Station, NJ) are nonstructural serine (NS3/4) protease inhibitors and the first DAAs approved for use in the United States and European Union, although many others are in the pipeline. The combination of DAAs, PEG-IFN, and RBV (triple therapy) substantially increases the rate of sustained virologic response (SVR) in treatment-naïve and -experienced patients.

Boceprevir and telaprevir stop HCV replication by inhibiting the NS3/4 protease, which is required for processing of the HCV polyprotein. These agents mimic the carboxy-terminal end of the NS3 protease and thereby interfere with formation of the HCV polyprotein, which blocks HCV replication.[1] Although protease inhibitors are potent antiviral agents, they must be given in combination with PEG-IFN and RBV to prevent the rapid selection of resistant variants.[2–4] Studies have shown that removal of RBV from the treatment regimen compromises efficacy, increasing the rate of virologic breakthrough.[5] Optimizing the rates of SVR to these drugs requires strategies to promote appropriate use and to avoid misuse of these drugs.

Triple Therapy Increases Rates of SVR for All Populations

Five distinct phase 3 trials have been performed with boceprevir and telaprevir (Table 1). For treatment-naïve patients, the serine protease inhibitor therapy-2 (SPRINT-2)[6] trial examined the effects of PEG-IFN α-2b, RBV, and boceprevir, whereas the A new direction in HCV care: astudy of treatment naïve hepatitis c patient with telaprevir (ADVANCE)[7] and illustrating the effects of combinatherapy with telaprevir (ILLUMINATE)[8] studies investigated the effects of PEG-IFN α-2a, RBV, and telaprevir. Treatment-experienced patients were included in

Abbreviations used in this paper: ADVANCE, a new direction in HCV Care: a study of treatment naïve hepatitis C patient with telaprevir; DAA, direct-acting antiviral; eRVR, extended rapid virologic response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ILLUMINATE, illustrating the effects of combinatherapy with telaprevir; LLQ, lower limit of quantification; LOD, limit of detection; PEG-IFN, peginterferon; RBV, ribavirin; REALIZE, the retreatment of patients with telaprevir based regimen to optioutcomes; RESPOND-2, retreatment with HCV serine protease inhibitor boceprevir and pegintron/rebetol-2; RGT, response-guided therapy; SOC, standard of care; SPRINT-2, serine protease inhibitor therapy-2; SVR, sustained virologic response.

0016-5085/$36.00
doi:10.1053/j.gastro.2012.02.013

Table 1. Summary of Phase 3 Clinical Trials for Boceprevir and Telaprevir

Study	Drug	Population	Treatment arm(s)	Intervention SVR	SOC SVR	Main findings
SPRINT-2[6]	Boceprevir	Naïve	Black			RGT therapy as effective as 48 weeks of therapy for non-black patients
			RGT	42%	23%	
			48-week therapy	53%		
			Non-black			~1/2 of patients eligible for RGT
			RGT	67%	40%	
			48-week therapy	68%		
ADVANCE[7]	Telaprevir	Naïve	T8 (pooled 24- and 48-week total therapy)	69%	44%	12-week telaprevir regimen preferable to 8-week regimen
			T12 (pooled 24- and 48-week total therapy)	75%		
ILLUMINATE[8]	Telaprevir	Naïve	T12 overall	75%	N/A	24-week total therapy for eRVR patients non inferior to 48 weeks of therapy
			eRVR + 24-week therapy	92%		
			eRVR + 48-week therapy	88%		~2/3 of patients eligible for shorter duration of therapy
RESPOND-2[9]	Boceprevir	Treatment experienced	RGT		Relapsers	Null responders excluded
			Prior relapsers	69%	29%	
			Prior nonresponders	40%		
			48 weeks		Nonresponders	Relapsers had similar outcomes as naïve population
			Prior relapsers	75%		
			Prior nonresponders	52%	7%	
REALIZE[10]	Telaprevir	Treatment experienced	T12 (48-week total therapy)			Relapsers had similar outcomes as naïve population
			Prior relapsers	86%	24%	
			Prior partial responders	57%	15%	
			Prior null responders	31%	5%	

eRVR, extended rapid virologic response; RGT, response guided therapy; SOC, standard of care; SVR, sustained virologic response, T8, 8-week telaprevir arm; T12, 12-week telaprevir arm.

retreatment with HCV serine protease inhibitor boceprevir and pegIntron/rebetol-2 (RESPOND-2) study,[9] in which they received boceprevir, and in the retreatment of patients with telaprevir based regimen to optimize outcomes (REALIZE) study,[10] in which they received telaprevir. Each trial reported improved efficacy compared with the standard of care (SOC) and demonstrated the opportunity to increase rates of curing HCV infection and shortening the duration of therapy for selected patients.

SPRINT-2 included separate cohorts of black and non-black patients and had a 4-week lead-in phase, in which patients were given PEG-IFN α-2b and RBV before triple therapy was initiated with boceprevir. Patients were randomly assigned to groups given either the SOC (48 weeks of PEG-IFN α-2b and RBV), boceprevir for 44 weeks with a fixed duration of PEG-IFN α-2b and RBV, or response-guided therapy (RGT), in which they received 24 weeks of boceprevir in a total treatment duration of 28 weeks. Patients who received RGT and had an undetectable level of HCV RNA at weeks 8 and 24 received no further therapy. If HCV RNA was detected, they received PEG-IFN α-2b and RBV, plus a placebo, for an additional 20 weeks (total treatment duration of 48 weeks). In the non-black patients cohort, patients in the fixed duration treatment group had an SVR rate of 68%, comparable with those who received RGT (67%), whereas the SVR rate in the control arm was only 40%. The rates of SVR following treatment with boceprevir were lower in the black than in the non-black patients cohort; there was a numerical but not statistically significant difference between the groups that received RGT and those that received 48 weeks of treatment, possibly because of the small number of patients in the black patients cohort (Table 1).

The ADVANCE and ILLUMINATE studies investigated triple therapy with a combination of telaprevir, PEG-IFN α-2a, and RBV (Table 1). Patients in the ADVANCE trial were randomly assigned to groups given 12 weeks of triple therapy, 8 weeks of triple therapy, or the SOC. Patients who received triple therapy continued PEG-IFN α-2a and RBV for a minimum duration of 24 weeks, whereas therapy was stopped for patients with extended rapid virologic responses (eRVRs; undetectable levels of HCV RNA at weeks 4 and 12). All others continued to receive PEG-IFN and RBV through week 48. Patients treated with 12 weeks or 8 weeks of telaprevir had significantly higher rates of SVR (75% and 69%, respectively) than the SOC group (44%).[7]

The ILLUMINATE study was designed to confirm that shortened treatment duration, based on response-guided principles, was not inferior to fixed treatment duration for patients who achieved eRVRs. All patients were initially treated with triple therapy that included telaprevir. Those achieving eRVRs were randomly assigned to groups that were given 12 or 36 additional weeks of PEG-IFN and RBV (total treatment duration of 24 weeks or 48 weeks). Among patients who achieved an eRVR (65%), the rates of SVR were similar after 24 or 48 weeks of therapy (92% and 88%, respectively). Therapy can therefore be shortened for a substantial number of patients, without compromising efficacy.[8]