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Educational Workshop
New direct-active antiviral agents for hepatitis C virus infection in previous treatment failure patients

A significant proportion of patients will not achieve an SVR with the previous SoC treatment consisting of pegylated interferon + ribavirine due to virological failure. These patients can broadly be divided into three groups: I Virological relapse:Virological partial response: Virological null response. Studies have now been conducted using boceprevir (B) and telaprevir (T) in these patients who have not achieved an SVR despite prior treatment. In the RESPOND-2 study using B, patients with previous relapse and partial response were recruited. All patients received treatment for 4 weeks with SoC Peg IFN-Alpha2b 1.5 µg/kg weekly and ribavirine 600-1400 mg daily. Patients were then randomized: Group 1 [control (total 48 weeks)] and Group 2 [response-guided therapy for 32 additional weeks (up to week 36); Group 3 (SoC for an additional 44 weeks). Overall SVR rates were Group 1 (control) = 21%, Group 2 (response-guided therapy) = 59% and Group 3 = 66%. Subgroup analysis indicated SVR rates among patients with previous relapse of 29% vs. 69% vs. 75% and among patients with previous partial response of 7% vs. 40% vs. 52% in favour of treatment with three agents. In the REALISE study using T, patients were randomized to three groups: PR48 (control group receiving SoC PR daily for 48 weeks), T12PR48 (SoC for 48 weeks with T treatment for the first 12 weeks) and lead-in T12PR48 (4 weeks lead-in with SoC followed by 12 weeks triple therapy, then continuation on SoC for a total of 48 weeks). Overall SVR rates were PR48 = 17%, T12PR48 = 64% and lead-in T12PR48 = 66%. Subgroup analysis indicated SVR rates (PR48 vs. T12PR48 vs. lead-in T12PR48) among patients with prior relapse of 24% vs. 83% vs. 88%; among patients with prior partial response of 15% vs. 59% vs. 54%; and among patients with prior null response of 5% vs. 29% vs. 33% (Table). In summary, there is a significant benefit to retreating patients who have previously had virological failure using triple therapy with a protease inhibitor. Overall, this can improve SVR rates in these patients by over 40%. The benefits of protease inhibitor regimens over SoC treatment seem to hold for patients with prior relapse, partial response and null response, although the SVR rate is lower in prior partial responders and null responders. The regimens used for B and T differed between the studies, but showed similar SVR rates. Of note, B has not been used in patients with a prior null response.

Drug	Boceprevir						Telaprevir								
Trial	RESPOND-2						REALISE								
Previous response	Relapse			Partial response			Relapse			Partial response			Null response		
	Group 1	Group 2 (RGT)	Group 3 (48 weeks)	Group 1	Group 2 (RGT)	Group 3 (48 weeks)	PR48	T12 PR48	Lead-in T12PR48	PR48	T12 PR48	Lead-in T12PR48	PR48	T12 PR48	Lead-in T12PR48
SVR	29%	69%*	75%*	7%	40%*	52%*	24%	83%*	88%*	15%	59%*	54%*	5%	29%*	33%*
Relapse	NR	NR	NR	NR	NR	NR	65%	7%†	7%†	N/A	21%	25%	60%	27%†	25%†

Summary of the SVR and relapse rates, where quoted, from the stated clinical trials for the addition of boceprevir or telaprevir to SoC therapy for Genotype 1 HCV-infected patients who have had prior virological failure with treatment. Patients are divided into those with prior relapse (undetectable HCV RNA at the end of treatment but do not achieve an SVR), prior partial response (≥ 2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment but never achieve undetectable HCV RNA) or prior null response (≤ 2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment). Shaded columns indicate control groups receiving SoC treatment alone. Relapse is defined as undetectable HCV RNA at end of treatment, but detectable within 24 weeks of follow-up. Study design and treatment groups are summarised in the text. Statistical analyses are compared with SoC treatment alone. HCV, hepatitis C infection; NR, No data reported; RGT, response-guided treatment; SVR, sustained virological response.

* $P < 0.001$.

† No *P*-value reported.