Favorable Adverse Event Profile of Sofosbuvir/Ribavirin Versus Standard of Care for Hepatitis C.

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BACKGROUND

- Triple therapy of pegylated interferon and ribavirin with Boceprevir (BOC) or Telaprevir results in improved SVR rates, however adverse events (AEs), pill burden and drug interactions remain significant barriers to successful completion of treatment
- The treatment of hepatitis C virus (HCV) infection is rapidly evolving to IFN free treatment with directly acting antiviral agents (DAAs) with the recent approval of Sofosbuvir (SOF).
- Objective

To evaluate the AEs observed with BOC/IFN/RBV therapy compared to sofosbuvir + ribavirin (SOF/RBV) in HCV monoinfected, genotype-1 (GT-1) individuals.

METHODS

- A retrospective review of clinical data from 2 cohorts of HCV monoinfected, GT-1 individuals who underwent treatment for HCV was performed.
  - Veterans Affairs Medical Center, Baltimore : tx naïve & experienced individuals with BOC/PEG-IFNα/RBV per package insert (n=97)
  - NIAID, NIH, Bethesda: SPARE trial of tx naïve individuals with SOF + weight based (1000 / 1200mg RBV daily) (n=35) or low dose (600mg RBV daily) (n=25)
- AEs namely hematologic, hepatic and renal were graded from 1 (mild) to 4 (severe) using the Division of AIDS toxicity table (version 1.0).
- Statistical analysis : nonparametric Wilcoxon rank sum , Chi square tests (GraphPad Prism 6.0) and multivariate logistic regression was performed.

RESULTS

- Baseline characteristics are shown in Table 1.
- Treatment with BOC/IFN/RBV was associated with a higher prevalence of adverse events namely anemia, neutropenia, thrombocytopenia and increased creatinine (Figures 1 & 2, Table 2).
- A higher proportion of patients in the BOC/IFN/RBV cohort required a RBV dose reduction, EPO, and or G-CSF before or at 24 weeks (Table 3).
- The multivariate logistic regression model showed lower odds for hematologic toxicity in the SOF/RBV cohort compared to BOC/IFN/RBV namely:
  - Anemia: OR -3.21 (0.73) P < 0.0001
  - Neutropenia: OR -4.42 (1.15) P = 0.0001
  - Thrombocytopenia: OR -4.36 (0.0062) P = 0.002
- Overall, 5 (8%) patients treated with SOF/RBV discontinued treatment early but none for AEs. In the BOC/IFN/RBV cohort, 52 (53%) stopped early of which 34 (64%) were due to AEs, P < 0.0001 (Table 3).

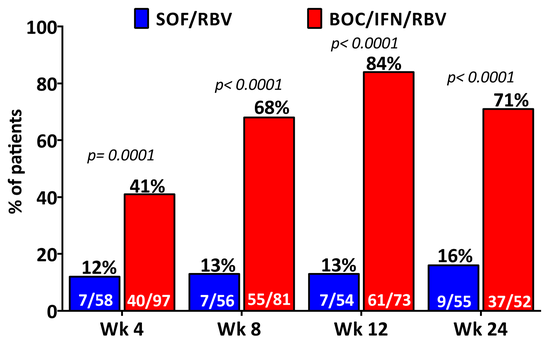
Table 1: Baseline Characteristics

Baseline Characteristics	SOF/RBV	BOC/IFN/RBV
* p<0.05	N (%) & Mean (Std)	
Age*	55 (8.4)	58 (5.7)
Black*	50 (83)	63 (65)
Male*	37 (62)	93 (96)
BMI	30 (6.5)	29 (6.0)
BMI ≥ 30	29 (48)	37 (38)
Fibrosis 3-4*	14 (23)	71 (77)
Log HCV VL	6.1 (5.5-6.5)	6.04 (0.67)
Hemoglobin*	13.7 (1.5)	14.48 (1.3)
Creatinine*	0.84 (0.2)	0.98 (0.2)
Absolute Neutrophil Count*	2.7 (1.7)	3.2 (1.4)
Platelets*	216.6 (70.7)	173 (65)
Total Bilirubin*	0.58 (0.32)	0.9 (0.4)

A limitation of this study was the imbalance in baseline covariates

Figure 1: Prevalence of Hemoglobin reduction over the course of treatment.

a) Incidence of Hgb Drop ≥ 3g/dL



b) Mean Hgb Decline

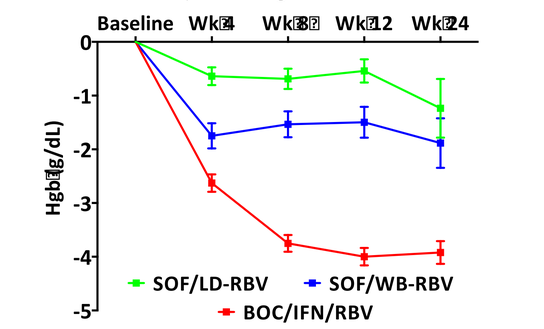
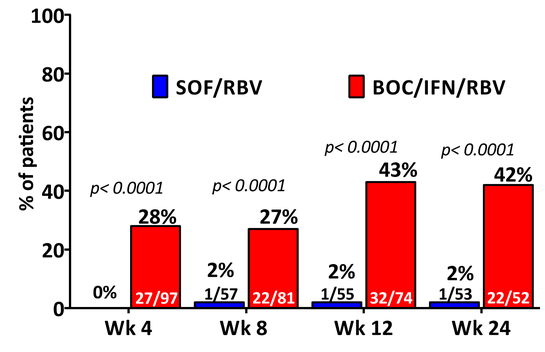


Figure 2: Prevalence of Neutropenia over the course of treatment



RESULTS

Table 2: Prevalence of Adverse Events During Treatment

Grading Event	Grade	SOF/RBV	BOC/IFN/RBV	P Value
		N (%)		
Anemia	0	44 (73)	27 (28)	< 0.0001
	1-2	15 (25)	60 (61)	
	3-4	1 (2)	13 (13)	
Neutropenia	0	59 (98)	26 (27)	< 0.0001
	1-2	0	46 (47)	
	3-4	1 (2)	25 (26)	
Thrombocytopenia	0	60 (100)	35 (36)	< 0.0001
	1-2	0	45 (45)	
	3-4	0	17 (17)	
Increased Creatinine	0	59 (98)	89 (92)	0.0427
	1-2	0	8 (8)	
	3-4	1 (2)	0	
Increased ALT	0	58 (97)	89 (92)	0.2205
	1-2	2 (3)	8 (8)	
	3-4	0	0	

Table 3: Participants Who Required EPO/G-CSF Or Early Discontinuation

	SOF/RBV	BOC/IFN/RBV	P Value
	N (%)		
Required RBV dose reduction before or at 24 Weeks?	10 (20)	64 (66)	< 0.0001
Required EPO before or at 24 weeks?	0	25 (26)	< 0.0001
Required G-CSF before or at 24 weeks?	0	12 (12)	0.0036
Stopped Rx Before or at 24 Weeks?	5 (8)	52 (53)	< 0.0001
Stopped Rx Before or at 24 Weeks due to an AE?	0	34 (64)	< 0.0001

CONCLUSIONS

- SOF/RBV treatment was associated with fewer side effects than Peg-IFNα + RBV + BOC therapy appearing to be a safer and more tolerable alternative for HCV GT-1 subjects.
- Results show that emerging IFN/RBV free therapies may enhance patient adherence, allowing treatment of larger numbers of patients.

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