

## Interferon (IFN) Based Treatment of African Americans with Chronic Hepatitis C (CHC) in an Urban Clinic: Improving Response with Advances in Therapy

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### ABSTRACT

**AIM:** In this paper, we review the results of the addition of a direct acting antiviral (DAA) to dual therapy [Pegylated-Interferon (Peg-IFN)+Ribavirin (Riba)] therapy in African Americans (AA) treated for chronic hepatitis C (CHC) in an urban GI clinic as compared to the licensing studies.

**METHODS:** Patients with genotype one (G1) CHC treated with dual therapy ( $n=341$  naïve patients), were compared to G1 patients ( $n=75$  naïve or previously treated with interferon based therapy) treated with triple therapy (telaprevir or boceprevir +Peg-IFN+Riba). Treatment response was assessed for both intent to treat and patients completing at least 12 weeks of therapy (protocol).

**RESULTS:** The sustained viral response (SVR) for all patients completing treatment and the follow up period was significantly higher with triple therapy as compared to dual therapy (AA: 51% vs 24%; Cau 100% vs 36%). In interferon experienced patients, the SVR for triple therapy was better in patients who had relapsed as compared to non-responders or naïve patients. The response rate with triple therapy was also better across all stages of fibrosis. Despite the increase in side effects seen in patients with the addition of DAA, discontinuation rates were fewer for triple than for dual therapy.

**CONCLUSIONS:** The data confirms previous reports from the licensing trials that adding a 1<sup>st</sup> generation DAA to dual therapy in

the real world clinic setting provides a significant improvement in SVR in African Americans, regardless of whether the patients are naïve or treatment experienced. While treatment with these therapies are clearly beneficial for patients with advanced disease, the lower SVR rate for AA as compared to Cau presents a challenging situation and that waiting for more effective therapies may be a prudent option for the majority of patients.

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**Key words:** Hepatitis C; Interferon-alpha; Ribavirin; Telaprevir; Boceprevir; African Americans

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### INTRODUCTION

More than 3.2 million people in the United States (1% of the population) are chronically infected with hepatitis C virus (HCV) and thus exposed to significant risk of developing HCV related morbidity and mortality<sup>[1-6]</sup>. African Americans (AA) are twice as likely to be infected with HCV compared to the non-Hispanic-white US population (Cau) and in addition, have a lower response rate to approved IFN based therapies<sup>[7-12]</sup>. Studies focusing on this population provide useful information with respect to the efficacy of new therapies and decisions to treat this historically low response rate group. Such studies are of importance since many clinical trials overestimate the response of AA patients treated in community settings.

Sustained viral response (SVR) to interferon based therapies is associated with decreased liver related morbidity and mortality in patients with HCV infection and the development of more effective

treatments is a continuing clinical goal<sup>[13,14]</sup>. The mainstay of current therapies is pegylated-IFN-alpha (peg-IFN) which is given by injection and ribavirin (riba) which is an oral medication associated with significant anemia. Over the past three years, addition of direct acting antivirals (telaprevir and boceprevir) has enhanced the response rates, but the medications also increased the anemia associated with IFN and ribavirin and, brought additional side effects including dysgeusia, severe rash and anal symptoms<sup>[15-19]</sup>. This study focuses on African Americans and compares the SVR, side effects and discontinuation rates seen with dual therapy (peg-IFN+ribavirin) vs first generation DAAs (telaprevir and boceprevir) given with triple therapy (peg-IFN+riba). The study presents data from both AA and Cau patients with chronic hepatitis C (CHC) who were seen in an urban clinic environment.

## METHODS

Based on medical records from 1995 to 2013, complete data on 416 CHC patients (AA=341; Cau=75) who were treated with interferon based therapy was collected. Patients were seen in an Urban GI clinic at Wayne State University School of Medicine. The majority of patients (AA= 275 Cau=68) were treated with dual therapy (Peg-IFN+Ribavirin) while the more recent patients (AA=68 and Cau=7) were treated with triple therapy (telaprevir or boceprevir with Peg-IFN+Rib). The objective of this IRB approved study was to compare the responses in patients treated with dual therapy to those given triple therapy. All patients included in this study were genotype 1 and received at least 1 treatment with interferon based therapy. Treatment response was reported for all patients entering the study (intent to treat) and those completing at least 12 weeks of therapy, and who, if they were responders, were available for assessment following the end of therapy (EOT). For patients on dual therapy SVR was defined as a non-detectable HCV RNA 6 months after EOT. Triple therapy was response-guided with SVR defined as a negative PCR at 3-6 months after EOT. Statistical analysis was performed using the JMP software from SAS. Continuous numeric variables were assessed using ANOVA analysis and Nominal character variables using Pierson Chi-Square analysis. We used multivariate analysis for the patient populations to determine characteristics that predicted response to therapy prior to treatment.

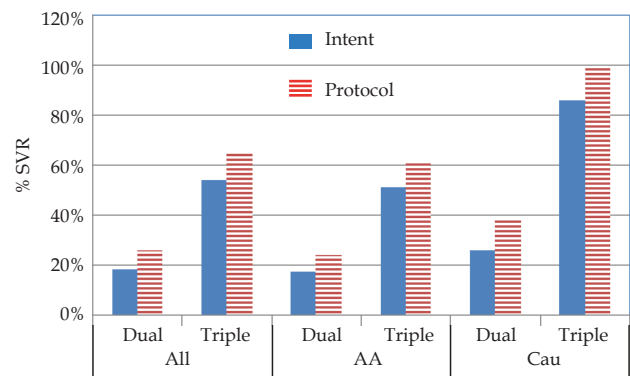
## RESULTS

As shown in table 1, the majority of patients seen in the clinic were AA (dual=81% and triple=90%). The age was slightly higher in the patients treated with triple therapy, consistent with either the predicted “aging” of the infected population or selection of patients with more advanced disease for treatment. Body weight was similar and using current definitions, the majority was in the overweight to obese

category. Platelet counts were well within normal limits. ALT levels were elevated in both treatment groups (83±71 vs 82±51 U/L (mean±SEM)) with 65% of the patients having an ALT that was greater than 60 U/L. In patients who had liver biopsy, fibrosis scores were also similar between the two treated groups although in the triple therapy groups, many of the biopsies were performed more than 2 years prior to initiating treatment. The levels of HCV RNA by PCR were significantly higher in the triple therapy group (5.0×10<sup>6</sup> vs 1.6×10<sup>6</sup> IU/mL). The reason for this difference is not known.

Response to therapy was evaluated for both the overall and the racial sub groups since studies have suggested that AA were less likely to respond than Cau for both dual and triple therapy<sup>[10,15,16]</sup>. Responses are reported for both Intent to treat (Intent) and for patients completing at least 12 weeks of therapy (Protocol). As shown in figure 1, triple therapy response was always significantly better than dual therapy (*P*<0.001) regardless of race. AA had a lower response than Cau regardless of the therapy (SVR based on protocol response for dual therapy (24% vs 36%, *p*=0.13 respectively) and for triple therapy (60% vs 100% , *p*=0.06 respectively).

Dual therapy patients were all naïve to treatment whereas triple therapy was approved for treatment-experienced patients as well as naïve. Comparison between previously treated and non treated patients could thus be assessed for triple therapy. As shown in figure 2, naïve AA with CHC treated with triple therapy had a better response rate than naïve AA treated with dual therapy. Nonresponders to previous therapy treated with triple therapy were not significantly different in response rates when compared to triple therapy treated naïve patients, Patients who had relapsed after successful ETR responded better to triple therapy than either naïve or nonresponders (83% compared to 40% and 46% *p*<0.05).



**Figure 1** Comparison of SVR Response to Dual vs Triple Therapy for AA vs Cau Patients. Triple therapy treated patient SVR are always greater than dual treatment (*p*<0.001). Caucasian response is always greater than AA but the numbers of Caucasians in the study are low and differences are not statistically significant. Intent includes all patients while protocol includes only patients who completed 12 weeks of therapy.

**Table 1** Patient Demographics and Baseline Characteristics by Race.

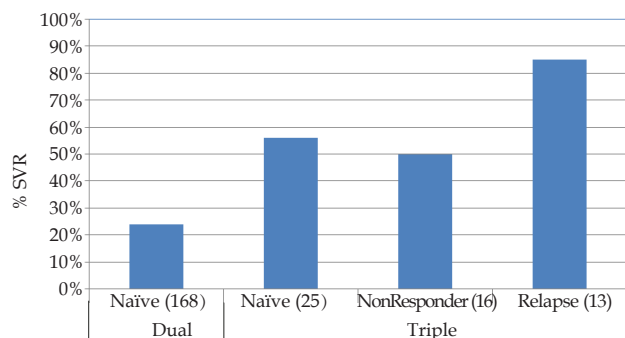
Parameters	All Patients				N	African Americans			N	Caucasians		
	N	Dual	N	Triple		Dual	N	Triple		N	Dual	N
Race (AA)	341	81%	75	90%								
Gender (Male)	341	56%	75	59%	275	55%	68	57%	66	60%	7	71%
Age <sup>1</sup> (years)	341	53±7	75	57±8	275	54±6	68	58±7	66	50±9	7	51±12
BMI (kg/m <sup>2</sup> )	318	30±7	75	30±6	258	30±6	68	31±6	60	29±8	7	30±6
Platelets (platelets/mL)	332	216±71	72	213±72	271	220±68	66	215±73	61	202±83	6	189±55
ALT (U/L)	337	83±72	72	81±50	273	80±61	66	79±51	64	99±102	6	94±42
Fibrosis (Metavir)	327	2.1±1.2	75	2.0±1.2	262	2.1±1.2	67	2.1±1.3	64	2.4±1.2	6	1.7±1.0
HCV <sup>1</sup> RNA(IU/mL)	342	1,634,000± 2,693,000	76	5,089,000± 5,967,000	275	1,617,000± 2,047,000	68	4,634,000± 4,889,000	66	1,709,000± 4,502,000	7	9,509,000± 12,129,000

<sup>1</sup> *P*<0.001 for Dual vs Triple.

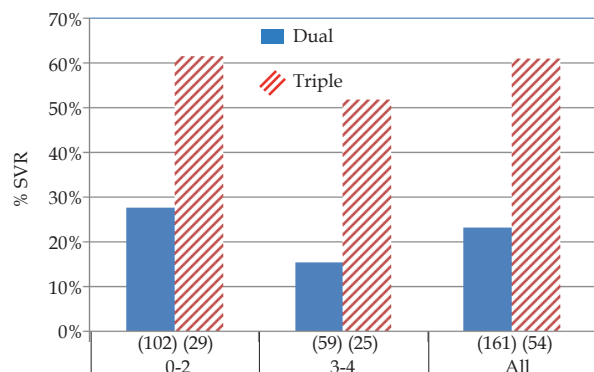
As shown in figure 3, triple therapy in AA patients enhanced the viral elimination rate at all stages of fibrosis when compared to AA treated with dual therapy. There was no statistically significant difference between the response rate of early fibrosis (0-2) vs late fibrosis (3-4) (27% vs 15% for dual and 62% vs 52% for triple).

Using multivariate analysis (Table 2) for the entire patient populations, low baseline virus levels were the dominant predictor of response to dual therapy ( $p<0.0001$ ) and Caucasian race ( $p<0.04$ ) was a less dominant predictor. For triple therapy, race (Cau), gender (F), previous treatment (Relapser) and baseline ALT (low) were all similar but weak predictors ( $p<0.02$ ). When the analysis was limited to only AA patients, the results were similar, confirming that the large number of AA patients was driving the statistical analysis. When the two parameters frequently used for assessing early response were evaluated, early viral decline ( $p<0.0001$ ) and a decrease in ALT ( $p<0.05$ ) was predictive of sustained response in patients receiving dual therapy. Neither was an early predictor of sustained response to triple therapy.

As predicted from the literature and the FDA approved drug inserts, triple therapy appeared to increase the incidences of anemia as defined by low hemoglobin and neutropenia and added new side effects which included pruritus, dysgeusia and anal symptoms (Table 3). Although the number of Cau treated with triple therapy was small, anemia (34% vs 14%) and especially pruritus (60% vs 14%) appeared to be more prominent in AA than Cau. Despite the challenges of increased side effects, patients in the triple therapy were less likely to discontinue than those in dual therapy (26% vs 17%).



**Figure 1** SVR for African Americans treated with dual or triple therapy based on whether patients were naive or previously treated with interferon based therapy. The number in parenthesis represents the patients completing protocol. (Naive dual <naive triple  $p<0.01$ ; Naive/NonResponder < Relapse  $p<0.05$ ).



**Figure 3** Fibrosis and SVR (protocol) response to therapy for AA Patients. The patients are stratified as indicated on the x axis as either F0-F2 (low fibrosis) or F3-F4 (high fibrosis). All represents the overall responses for all patients with a biopsy. The number in parenthesis represent the total number of patients in each group with a biopsy for fibrosis prior to treatment. Dual was significantly less than triple for each stage ( $p<0.05$ ). Both dual and triple did not have a statistically significant difference between stages of fibrosis.

**Table 2** Multi-variant Analysis of Baseline Predictive Values of SVR Response.

Parameter	Dual (value is probability <chi-square)		Triple (value is probability <chi-square)	
	ALL	AA	ALL	AA
Age	0.06	0.08	0.08	0.08
Gender (female)	0.89	0.45	0.01*	0.01*
Race (Cau)	0.04*		0.01*	
BMI	0.75	0.84	0.11	0.11
Previous Treatment (relapse)			0.02#	0.02*
Stage of Fibrosis	0.11	0.10	0.48	0.48
Baseline PLT	0.55	0.93	0.09	0.10
Baseline PCR (lower)	0.0001*	0.001*	0.92	0.92
Baseline ALT (lower)	0.95	0.51	0.01*	0.01*

\*Significant independent factors for predicting response.

**Table 3** Side effect profiles for Dual vs Triple Therapy for All Patients by Race.

		Dual Therapy		Triple Therapy		
		No.	%	No.	%	
Anemia (by hemoglobin)	AA (275)#	47	17%	AA (275)#	47	17%
	Cau (66)	8	12%	Cau (66)	8	12%
	All (341)	55	16%	All (341)	55	16%
Neutropenia	AA (275)	6	2%	AA (275)	6	2%
	Cau (66)	1	2%	Cau (66)	1	2%
	All (341)	7	2%	All (341)	7	2%
Pruritus	AA (275)	0	0%	AA (275)	0	0%
	Cau (66)	0	0%	Cau (66)	0	0%
	All (341)	0	0%	All (341)	0	0%
Dysgeusia	AA (275)	0	0%	AA (275)	0	0%
	Cau (66)	0	0%	Cau (66)	0	0%
	All (341)	0	0%	All (341)	0	0%
Anal Symptoms	AA (275)	0	0%	AA (275)	0	0%
	Cau (66)	0	0%	Cau (66)	0	0%
	All (341)	0	0%	All (341)	0	0%

# Numbers in parenthesis indicate total number of patients in the study; \* & Pruritus was more frequent in AA than Cau.

## DISCUSSION

This study supports previous reports from the licensing studies that adding a DAA to peg-IFN and riba (triple therapy) increases the SVR for African American patients treated in an urban clinic as compared to peg-IFN and riba (dual therapy). One reason these studies are important is that clinical trials often do not include large numbers of AA since they represent only 13% of the population. For example, pooling of the patients treated in phase 3 studies with telaprevir in combination with pegylated interferon alpha (peg-IFN) and ribavirin (riba) as compared to dual therapy (peg-IFN+riba) was required in order to generate sufficient number of AA for comparison (127 AA and 1,124 Cau)<sup>[11,12,18-20]</sup>. The responses reported in the study for AA with triple therapy was higher than for dual therapy [(62% ( $n=99$ ) vs 29% ( $n=28$ )). In Cau the responses were also greater for triple vs dual therapy but were also greater than for AA [78% ( $n=791$ ) vs 47% ( $n=333$ )]. Thus while triple therapy was better than dual therapy for both races, the overall response rate for dual and triple therapy is biased by the large numbers of higher responding Caucasians and therefore misleading with respect to the response of individual African Americans. Thus, the data in our study demonstrates that even in the harder to treat population (AA with genotype 1) who are the predominant population seen in our clinic, the overall protocol response rates of 51% vs 24% was a significant improvement in SVR. In the hardest to treat population, treatment experienced non-responding AA with genotype 1, the response rate was still 46%. The

maximum response was seen in previous responding patients where SVRs approaching 83% were achieved.

Since many of the patients have been infected for a considerable period of time, they have an increasing risk of advanced fibrosis, cirrhosis and hepatocellular carcinoma<sup>[3,5]</sup>. Treating these patients with advanced fibrosis is critical, but responses were poor for dual therapy. When response rate to dual therapy was compared to responses to triple therapy, all stages of fibrosis (F0 to F4) benefited when comparing response of dual to triple therapy.

In comparing the factors that biased patients towards enhanced response, we found that viral load was more of a factor with respect to failure for dual therapy than triple therapy. AA had lower responses for both therapies compared to Cau, and, in multivariate analysis, race was a factor in both dual and triple therapy.

The side effect profiles for both therapies were similar to those reported for the licensing trials. DAA addition enhanced the anemia known to be due to ribavirin and added the additional side effects of pruritus, dysgeusia and anal symptoms. With respect to race, AA had higher rates of pruritus (65%) than Cau (14%) but the number of Cau in our study was low. While significant numbers of patients did experience side effects, they were generally mild and medically manageable. This was especially true for the anemia which in triple therapy could be handled by reducing the ribavirin without having a negative impact on the impressive improvement in response compared to dual therapy. Although there were considerably more side effects associated with the triple therapy, discontinuation rates were lower. Whether this represents better management, greater incentive to continue due to the fast decline of viral load in the majority of patients or other factors is not known.

This study is important due to the demonstration in a predominately African American population in a real world clinic population, that there is significant improvement in the response of African Americans to triple therapy as compared to dual therapy. A weakness in this study is that the clinic population is predominately African American and since few Caucasians are seen in the clinic, there were significantly fewer Caucasians in the triple therapy group as compared to the dual therapy group.

## CONCLUSIONS AND RECOMMENDATIONS

While the response rates are better for AA patients treated with triple therapy as compared to dual therapy, it remains less than 50% for the majority of patients seen in our clinics. Consistent with the observation that licensing trials may not predict the response of a difficult to treat minority population, this response is lower than predicted based on the small number of AA in the licensing trials. Thus it is imperative that the AA population, many of whom have advanced liver disease, be afforded rapid access to the next generation therapies. These therapies will predictably increase the SVR in this previously difficult to treat group.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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