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Comparative Effectiveness of Telaprevir-Based Triple Therapy in Patients with Chronic Hepatitis C

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Abstract

Background/aim—To examine the effectiveness and tolerability of triple therapy with pegylated interferon (p-IFN), ribavirin (RBV) and telaprevir (TPV) in chronic hepatitis C (CHC) patients treated in an academic practice setting, among a more clinically diverse population than was treated in phase 3 trials.

Methods—A prospective database of all viral hepatitis patients undergoing antiviral therapy from January 1, 2006 – July 1, 2012 was queried to identify treatment naïve and experienced CHC patients treated with dual and triple therapy. On-treatment response categories included: rapid virologic response (RVR), extended rapid virologic response (eRVR), early virologic response (EVR), and sustained virologic response (SVR). These patients were compared to matched controls, namely patients that underwent dual therapy with p-IFN and RBV. Matching was performed for age, cirrhosis status and history of previous treatment.

Results—There were 55 patients treated with triple therapy who met the eligibility criteria, consisting of treatment-naïve (n=35) and-experienced (n=20, relapse=9, non-response=9, and previous early-terminators n=2). RVR was achieved in 41%, eRVR in 41% and EVR in 75%. SVR was observed in 51% of treatment naïve patients, 67% of non-responders, and 56% of those with prior relapse. Corresponding results after dual therapy were 37%, 11% and 27%, respectively. The mean drop in hemoglobin at weeks 4, 8 and 24 of triple therapy were 2.8 mg/dl, 3.8 mg/dl and 3.2 mg/dl, compared to 2.4 mg/dl, 2.6 mg/dl and 2.4 mg/dl with dual therapy.

Conclusion—Telaprevir triple therapy in clinical practice is more effective than p-IFN/RBV dual therapy despite the significant degree of anemia that complicated therapy requiring RBV dose reduction and erythropoietin support.

Introduction

Chronic hepatitis C virus (HCV) infection affects more than 170 million people worldwide ¹. In the United States, over 4 million Americans are estimated to have had the infection ². The long term outcomes of chronic HCV infection may be serious and dire, including complications such as cirrhosis, liver failure, or hepatocellular carcinoma ³. HCV-

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related liver disease remains the leading indication for liver transplantation. Effective interventions are critically needed to curb these long term consequences of chronic HCV infection.

Until recently, dual therapy with pegylated interferon (p-IFN) and ribavirin (RBV) represented the standard of care for over a decade. The dual therapy was limited because of suboptimal efficacy and frequent occurrence of adverse events leading to dose reduction, intolerance, and premature termination of therapy. The efficacy of the dual therapy in registration trials ranged from 40% to 70% depending on the genotype, but effectiveness in community and practice setting has been reported to be lower^{4,5}. Participation in phase 3 clinical trials is restricted to a relatively robust patient population in terms of proximity to the treating center, age, chemical dependency and comorbidities. In addition, on-treatment progress in phase 3 clinical trials, e.g. dose adjustments in response to efficacy and adverse events, are carefully monitored and executed with the support of clinical research organizations and a carefully developed protocol. For these reasons, efficacy and tolerability observed in late phase clinical trials may not be fully reproducible in more diverse patient populations undergoing treatment in less tightly controlled circumstances.

Telaprevir is one of the two NS3/4A ('first generation') protease inhibitors that were approved in 2011 to be used in conjunction with p-IFN and RBV in patients with chronic hepatitis C with genotype 1^{6,7}. In registration trials, the efficacy of triple therapy regimens including telaprevir has been reported to be significantly higher than dual therapy. However, both of the first generation protease inhibitors have their own set of adverse effects, as well as other limitations such as pill burden, difficult dosing schedule and susceptibility to emergence of viral resistance.

In this study, we describe the comparative effectiveness of the triple versus dual antiviral regimens for chronic hepatitis C in an academic clinical practice. We examine viral response during and after completion of therapy, as well as adverse events, treatment discontinuation and dose reduction in patients who underwent telaprevir-containing triple therapy in comparison to the conventional dual therapy.

Methods

A prospective clinical database tracking all viral hepatitis patients undergoing antiviral therapy from January 1, 2006 – July 1, 2012 was queried to identify chronic hepatitis C patients who received antiviral therapy in an academic hepatology practice. All patients had detectable serum levels of HCV RNA and had historical or histological evidence of chronic HCV infection. While this database includes patients since the conventional interferon era, patients receiving dual combination of p-IFN and RBV accounted for the majority. When the first generation protease inhibitors were first approved, our hepatology group made a consensus decision to preferentially use telaprevir in part to gain experience rapidly with one agent. Dual and triple therapy regimens were according to the package insert of each agent and clinical practice guidelines without incorporating investigational tests such as IL-28b genotyping.

Patients who received at least one dose of telaprevir with intent to achieve SVR were identified and included in the triple therapy group. In comparison, matching subjects were selected among those who underwent dual therapy with p-IFN and RBV for genotype 1 or 4. These controls were matched by gender, age, fibrosis stage and history of previous treatment (naïve versus experienced). Subjects receiving telaprevir were matched in a 1:2 fashion to subjects receiving dual therapy using age (matched $\pm$ 5 years) and exact matches on gender, presence of cirrhosis, prior treatment and HCV genotype. Additional criteria for inclusion in this analysis consisted of the following: (1) verifiable date of treatment initiation and discontinuation; (2) provision of research authorization and (3) absence of co-infection with HIV or HBV.

From the database, the following pertinent information was extracted: demographic information, liver biopsy results, radiographic assessment of fibrosis/cirrhosis and laboratory results. The laboratory results included hemoglobin, WBC, platelets, and HCV RNA at treatment initiation and at weeks 4, 8, 12, 24 of treatment. Post treatment data up to 24 weeks post-completion were also obtained. Adverse events, therapeutic dose modifications, and treatment discontinuation were also identified.

In determining treatment response, the following definitions were used:

(1) rapid virologic response (RVR: negative HCV RNA at week 4); (2) early virologic response (EVR: negative HCV RNA at week 12); and (3) sustained virologic response (SVR: negative HCV RNA 12-24 weeks after cessation of therapy). For triple therapy recipients, extended RVR (eRVR) was defined as negative HCV RNA at weeks 4 and 12. Standard definitions were used to define non-response (never achieving HCV RNA-negative) and relapse (HCV RNA-negative at end of therapy with subsequent detectable HCV RNA). Patients who discontinued therapy before they reached appropriate therapeutic milestones, most commonly as a result of adverse events and intolerance were classified as early terminators. In conducting an intent-to-treat analysis, denominators were patients that could have reached each milestone, which was necessary for the triple therapy group, because not all patients were followed long enough to be assessed for SVR.

The primary endpoint of this study was the proportion of patients who had HCV RNA clearance at variable treatment points. Secondary endpoints addressed tolerability of the therapy – namely the proportion of patients experiencing adverse events, dose reduction and of early termination. Matched logistic regression was used to test comparisons between the telaprevir treatment group to the dual therapy group. Due to the difficulty in matching a few subjects, a sensitivity analysis was done by rerunning the logistic regression but ignoring the matched pairs and instead adjusting for the matching variables.

Results

Fifty-five patients received telaprevir-based triple therapy and met the inclusion criteria. Out of 900 patients who received dual therapy, 91 patients were matched according to the algorithm. While both treatment groups appeared comparable in the univariate analysis, when matched in a multivariate fashion, there were some telaprevir subjects who could not

be matched. For 36 triple therapy patients (65%), two controls were matched as intended, whereas in the remaining 19 triple patients, only one control could be matched.

Baseline characteristics of the two groups are summarized in Table 1. All of the patients had HCV genotype 1 except two in the triple therapy group and one in the dual therapy group who were infected with genotype 4. There was a higher proportion of prior non-response in the dual therapy group that did not reach statistical significance. Other characteristics that could potentially influence response were well matched including, the proportion of patients with cirrhosis, HCV RNA concentrations and blood counts.

Table 2 outlines the treatment outcomes for both groups. In the telaprevir group and prior to reaching 4 weeks of treatment, 4 patients discontinued therapy due to intolerance, resulting in 51 patients completing 4 weeks of treatment. Out of those patients, 41% (21/51) achieved RVR with a negative a HCV RNA. By 8 weeks, one more patient discontinued therapy with the remaining 50 patients on therapy while 6 more patients discontinued therapy due to intolerance after 8 weeks. All but four patients in the telaprevir group either reached the 24 week post-treatment milestone or discontinued therapy early due to intolerance.

Importantly, the overall SVR rate was significantly higher in the triple therapy group (53%) than that in the dual therapy group (31%, $P=.04$). The difference between the two groups seemed to be in the proportion of non-responders (7% versus 35%), whereas the proportion of patients who relapsed or terminate early appeared comparable. With regard to the four patients in whom the SVR status could not be determined, all achieved end of treatment response. One of the four patients was a rapid virological responder and the other three had EVR. There were four confirmed non-responders to the triple therapy, half of whom were null responders and the other half partial responders.

Table 3 summarizes the treatment response rates in the two groups based on previous treatment status. Numerically, the triple therapy group had a higher SVR rate than the dual therapy group in all categories, including treatment-naïve, prior non-responder and prior relapse patients. However, when a formal comparison was made assessing for an interaction between treatment group and prior treatment status, the difference did not reach statistical significance.

Table 4 summarizes the SVR rates in both groups in relation to cirrhosis status. There were a total of 24 patients with cirrhosis who underwent triple therapy. These patients had well compensated cirrhosis with a mean MELD score of 7 (6-12). SVR was achieved in 11 (46%) of these patients, 2 (8%) were non-responders, 4 (17%) had relapsed, 5 (20%) terminated the treatment early due to intolerance and 2 (8%) had end of treatment response but had not reached the 24 week post treatment milestone.. The reasons for treatment discontinuation were anemia (n=3) and neuropathy (n=2) in this group. The SVR rate of 46% in these patients was significantly higher than that in the dual therapy group.

Because of the difficulty in matching a few subjects, a sensitivity analysis was done by rerunning the logistic regression but ignoring the matched pairs and instead adjusting for the matching variables. The results of this analysis were similar to the matched analyses.

With regard to tolerance to therapy, nine of the triple therapy patients (16.4%) discontinued therapy due to intolerance. The reasons for discontinuation included symptomatic anemia (n=3), neuropathy (n=3), skin rash (n=1), nausea/vomiting (n=1), dyspnea (n=1), flu-like illness (n=1) and dizziness (n=1). In comparison, treatment was terminated early in 17 of the dual therapy group (18.7%) because of intolerance. The most common reason for discontinuation was psychiatric (n=5). Other factors prompting discontinuation included nausea/vomiting (n=3), anemia (n=2), financial (n=2), flu-like illness (n=2), thrombocytopenia (n=1), infection (n=1) and subarachnoid hemorrhage (n=1).

The mean pre-treatment hemoglobin level in the triple and dual therapy groups was 14.5 mg/dl and 14.6 mg/dl, respectively. Significant reduction in hemoglobin concentrations was noted across all categories of patients. In Figure 1, at four weeks of therapy, the hemoglobin level decreased to by a mean of 2.8 mg in the triple therapy group compared to a mean of 2.4 mg/dl in the dual therapy group. The nadir hemoglobin was observed in the 8th week (mean=10.7 mg/dl) in the triple therapy group, when the mean reduction in hemoglobin was 3.8 mg/dl compared to the pre-treatment level. In the dual therapy group, the nadir hemoglobin level was observed in the 20th week (mean 11.5 mg/dl), with the mean reduction being 3.1 mg/dl from pre-treatment level. Figure 2 shows that there was no noticeable difference in the degree of thrombocytopenia between the triple and dual therapy groups. There were three patients with a pre-treatment platelet count < 75,000. None of these patients, however, reached critical value (i.e., < 20k) throughout the treatment course. No patient experienced significant bleeding as a result of thrombocytopenia.

Dose modification of RBV was necessary in 23/55 patients (42%) in the triple therapy group. In contrast, dose modification occurred in 19/91 (21%) patients receiving the dual therapy ($P=.01$). Due to anemia, 11/55 (20%) of patients in the triple therapy group required erythropoietin, while 11/91 (12%) of patients in the dual therapy group required erythropoietin support ($P=.23$).

Discussion

In this study, we aimed to assess the effectiveness and tolerability of the triple therapy compared to dual therapy for chronic hepatitis C in an academic clinical practice. Effectiveness, as opposed to efficacy, addresses the extent to which an intervention is beneficial in real-life experience versus the effects experienced in the controlled setting of clinical trials. The main findings of our study were (1) the triple therapy led to SVR in at least 53% of patients in our practice, which was significantly higher than the 31% observed in matched historical controls; (2) treatment results were better in previously untreated and non-cirrhotic patients; and (3) triple therapy was associated with larger decrease in hemoglobin than dual therapy, but did not increase the rate of treatment discontinuation.

Multiple phase 3 trials have evaluated the efficacy of telaprevir-based triple therapy in different patient populations. The rate of RVR among treatment-naïve patients treated with telaprevir triple therapy in registration trials ranged between 66%-68%. The rate of eRVR was noted to be between 57%-58%. The SVR rate varied depending on the regimen used but ranged from 69%-75%⁸. The response rates were different among treatment-experienced

patients, as expected. The rates of RVR in that patient population were 26% and 70% in previous non-responders and relapsers, respectively. The SVR rates reported in treatment experienced patients were around 30% and 85% in previous non-responders and relapsers, respectively ⁹.

In analyzing the different subgroup responses of our patient population, we found that the SVR rate in the treatment-naïve triple therapy group was slightly lower than demonstrated in phase 3 trials, at 51% versus 69%-75% ⁸. Our prior non-responders seem to respond better to the telaprevir triple therapy than those in the registration trials, 67% versus 30%, whereas our previously relapsed patients had substantially lower SVR rates, 56% versus 85% ⁹. In addition to the usual factors that lead to different response rates in effectiveness compared to efficacy studies, we suspect that patient selection may have influenced our SVR rates. For example, the clinician may have recommended the triple therapy in prior relapse patients that were felt to be difficult-to-treat or in prior non-response patients that were deemed easier-to-treat, in light of other therapeutic options being developed. Newly approved agents such as Sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, is a promising direct antiviral therapy for CHC. Phase III trials have demonstrated an SVR rate of 100% in treatment naïve HCV patients with genotypes 2 and 3 when combined with ribavirin ¹⁰. Other phase III trials, however, have documented a much lower SVR rate in HCV genotype 3 patients at 56% and 61% ^{11,12}. Daclatasvir, an NS5A inhibitor, is another direct antiviral agent currently in phase III trials. Phase II trials have shown a promising SVR rate of 83% in genotype 1 HCV patients when combined with pegylated interferon and ribavirin ¹³. On the other hand, in our patients receiving dual therapy, SVR rates were comparable to those reported for the control groups in registration trials ⁸.

Interestingly, treatment discontinuation due to intolerance occurred more often in the dual therapy group than in the telaprevir group. The rate of discontinuation due to anemia was higher in the telaprevir group at 3.6% than the dual therapy group at 2.2%. Similarly, the degree of anemia observed was also more severe in the telaprevir group than the dual therapy group. This is also reflected in the higher percentage of patients who required dose modification in the telaprevir group. These data highlight the importance of close monitoring of the hemoglobin levels and proactive management for patients on telaprevir based therapy. It is important to note that even with dose modification, a high percentage of patients in the telaprevir group still able to clear the HCV RNA at their current treatment stage. This is contrasted to only 3/8 (37.5%) of patients who required dose modification in the dual therapy group who were able to achieve SVR.

Although anemia was one of the most common causes of treatment discontinuation, the most common reason for treatment discontinuation in the dual therapy group was psychiatric. None of the patients in the telaprevir triple therapy group required treatment discontinuation due to psychiatric side effects. It is likely that this also reflects patient selection. The clinicians, anticipating interferon-free regimen in the future, may have avoided recommending the triple regimen in patients who are at high risk of interferon intolerance. Finally, only 1/55 (1.8%) of patients in the telaprevir group discontinued treatment due to the development of a rash. This is lower than the rate of 4%-6% reported in the PROVE III trial ¹⁴.

In light of paucity of data examining the day-to-day clinical effectiveness and tolerability of telaprevir triple therapy, our data are one of the first to examine patients in routine clinical practice. Despite the reputation of Mayo Clinic as a referral center for patients from long distances, the majority of our practice is based on local/regional patients, especially those with chronic hepatitis C. We also believe that most practitioners that currently and actively treat patients with chronic hepatitis C have access to nursing staff and practice infrastructure that are not too different from ours. The data presented herein were collected prospectively according to an established management protocol, which minimizes biases that may be introduced in usual retrospective studies. On the other hand, this study is limited by its relatively small sample size, which may have resulted in type-II errors. In addition, a small number of patients who have not completed their intended duration of therapy, which may alter the ultimate response rates somewhat. Finally, there is likely a component of patient selection, because some patients from the dual therapy era had been held back in anticipation of the introduction of telaprevir, while others may still be advised to continue to wait for the next generation of medications. We believe the selection bias may be bidirectional and caution is advised in interpreting our data.

With recent approval of two additional agents for the treatment of chronic hepatitis C, the future of telaprevir triple therapy is uncertain. It is possible that our results may become obsolete in the near future. However, given the high treatment costs with the new therapeutic agents, there remains a possibility that protease inhibitors may continue to serve a segment of chronic hepatitis C patients, in part depending on healthcare delivery decisions by the payers of the US and other healthcare setting. It is conceivable that patients may be directed to protease inhibitor triple therapy if they are expected to respond well. These may include patients with favorable genotypic profile (e.g., IL-28b CC genotype) or patients who achieve RVR.

Conclusion

In conclusion, in an academic hepatology practice, telaprevir-containing triple therapy leads to successful viral eradication in a substantial proportion of patients with genotype 1 hepatitis C virus, and is significantly more effective than dual therapy. However, in achieving satisfactory response rates, the practitioner must be prepared to encounter a significant degree of anemia, even with RBV dose reduction and erythropoietin support. While patients and providers await interferon-free regimens, there may be a subgroup of patients who may be adequately managed with telaprevir-based therapy.

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Abbreviations

HCV	Hepatitis C virus
SVR	Sustained virologic response
RVR	Rapid virologic response
eRVR	Extended rapid virologic response

EVR	Early virologic response
p-IFN	Pegylated interferon
RBV	Ribavirin

Figure 1.

Figure 2.

Table 1
Baseline Characteristics

Characteristic	Triple Therapy (n=55)	Dual Therapy (n=91)	P-value
Male (%)	34 (62%)	55 (60%)	NA
Age in years (SD)	53.0 (9.9)	51.1 (9.0)	<0.01
Caucasians (%)	48 (87%)	80 (88%)	0.87
Genotype 1 (%)	53 (96%)	90 (99%)	0.99
Weight in Kg (SD)	87.6 (19.1)	87.3 (17.5)	0.83
Treatment Naïve (%)	35 (64%)	62 (68%)	0.99
Treatment Experienced (%)	20 (36.4%)*	29 (32%)	
Prior non-response (%)	9 (45%)	19 (68%)	
Prior relapse (%)	9 (45%)	9 (32%)	
Hemoglobin; mg/dl (SD)	14.7 (1.3)	14.6 (1.4)	0.57
White Blood Cells; $\times 10^3/\mu\text{L}$ (SD)	6.5 (2.0)	6.3 (1.8)	0.67
Platelets; $\times 10^3/\mu\text{L}$ (SD)	179 (71)	193 (65)	0.23
ALT	78 (53-149)	98 (66-125)	0.16
Bilirubin	0.6 (0.5-0.9)	0.6 (0.5-0.8)	0.32
HCV RNA; $\times 10^4\text{IU/ml}$ (range)	389 (140-1080)	159 (57-420)	0.02
Cirrhosis (%)	24 (44%)	49 (54%)	0.12

* 2 patients in the triple therapy group were previous early terminators of treatment due to intolerance.

Table 2
Treatment Outcomes

Treatment Outcome	Triple (n=55)	Dual (n=91)	P-value
SVR # (%)	29 (53%)	28 (31%)	0.04
Non-response # (%)	4 (7%)	32 (35%)	
Relapse # (%)	7 (13%)	14 (15%)	
Early termination # (%)	11 (20%)	17 (19%)	
Undetermined # (%) [*]	4 (7%)	NA	

^{*} Four patients did not reach 24 weeks post treatment. All four achieved end of treatment response.

Table 3
SVR In Relation to Prior Treatment Status

Prior Treatment Status	Triple (n=53) *	Dual (n=91)	P-value
Naïve # (%)	18/35 (51%)	23/62 (37%)	0.47
Prior Non-responder # (%)	6/9 (67%)	2/18 (11%)	
Prior Relapse # (%)	5/9 (56%)	3/11 (27%)	

* 2 patients in the triple therapy group were previous early terminators of treatment due to intolerance and not included in this table.

Table 4
SVR In Relation to Cirrhosis status

Cirrhosis Status	Triple (n=55)	Dual (n=91)	P-value
Cirrhotic	11/24(46%)	13/49 (27%)	0.03
Non-cirrhotic	18/31 (58%)	15/42 (36%)	
Overall	29/55 (53%)	28/91 (31%)	