ORIGINAL RESEARCH

Is Response-Guided Therapy Being Applied in the Clinical Setting? The Hepatitis C Example

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BACKGROUND: Response-guided therapy (RGT) is a treatment model that bases adjustments to therapeutic regimens on individualized patient physiologic response. This approach is applied to patients with chronic hepatitis C virus (HCV) infection who are treated with a triple therapy regimen of boceprevir or telaprevir in combination with pegylated interferon and ribavirin. As RGT expands in other pharmacologic regimens, including the treatment of breast cancer and acute myeloid leukemia, a measurement of how this approach is applied in clinical practice is important to determine whether the benefits of RGT are being optimized.

OBJECTIVE: To measure adherence to the RGT guidelines and to the treatment futility rules based on the drug labeling information for boceprevir and for telaprevir in the treatment of patients with chronic HCV infection.

METHODS: A retrospective observational cohort study was conducted using the large Humana research database, which includes pharmacy, medical, and laboratory claims, as well as enrollment data for more than 1.5 million fully insured commercial members, 1.9 million Medicare Advantage members, and 2.4 million Medicare Part D members from all 50 states. The study population included patients aged ≥18 years to <90 years who were fully insured with commercial or Medicare Advantage coverage. A pharmacy claim for boceprevir or telaprevir was used to identify patients receiving triple therapy for HCV infection. Medical, pharmacy, and laboratory claims were reviewed from the date of the first boceprevir or telaprevir pharmacy claim between May 2011 and February 2012 through a 32-week follow-up period, during which patients were required to have continuous health plan enrollment eligibility. This time period allowed for the occurrences of required HCV RNA laboratory monitoring and the assessment of treatment patterns. The use of RGT for boceprevir and telaprevir includes the monitoring of HCV RNA levels at routine intervals to determine how to proceed with therapy. Adherence to HCV RNA monitoring was measured as the proportion of eligible patients who had an HCV RNA assay at each of the recommended time intervals. According to futility rules, patients with greater-than-expected HCV RNA levels are deemed to be nonresponders and should discontinue therapy. Adherence to futility rules was measured as the proportion of patients who stopped therapy among all patients who had an HCV RNA result, which indicated treatment futility at each monitoring interval.

RESULTS: A total of 326 patients (65 in the boceprevir group; 261 in the telaprevir group) were eligible for the HCV RNA monitoring analysis, and 134 patients (20 receiving boceprevir and 114 receiving telaprevir) were eligible for the futility rules analysis. There were 1203 HCV RNA assays during the follow-up period. The percentage of patients who were adherent to HCV RNA monitoring during the entire treatment period was 29.2% in the boceprevir group and 32.2% in the telaprevir group. In both treatment groups, adherence to HCV RNA monitoring was highest at the first recommended time interval, followed by a downward trend in the second and third time intervals. Approximately 15% of 134 eligible patients met the futility rules for stopping therapy based on HCV RNA assay results, and 55% of those patients stopped the therapy in accordance with the treatment futility rules.

CONCLUSION: The implementation of RGT was suboptimal in this population of patients with chronic HCV infection; adherence to HCV RNA monitoring guidelines was less than 33%, and adherence to treatment futility rules was less than 50%. Managed care pharmacists should identify strategies to increase the adoption of RGT, which may, in turn, improve patient care and reduce unnecessary expenditures.

KEY WORDS: response-guided therapy, hepatitis C virus, boceprevir, telaprevir, pegylated interferon, RNA assay
Response-guided therapy (RGT) is a treatment paradigm that bases adjustments to therapeutic regimens on individualized patient physiologic response. Depending on a patient’s measured response to a drug, dosing may need to be adjusted accordingly or the therapy may need to be stopped altogether if the continuation of that treatment is deemed futile. As personalized medicine and waste reduction become mainstays of drug therapy, RGT is progressively being utilized in pharmacologic regimens for diseases such as breast cancer and acute myeloid leukemia. The implementation of an RGT approach to drug therapy has been used with boceprevir and telaprevir, and is being investigated with simeprevir in the treatment and management of chronic hepatitis C caused by persistent hepatitis C virus (HCV) infection. An understanding of how RGT is being applied in clinical practice is paramount for realizing the potential benefits of the approach.

In 2011, boceprevir and telaprevir, each in combination with pegylated interferon and ribavirin, became first-line recommended treatments for HCV genotype 1a, based on clinical trials demonstrating an increase in sustained virologic response of approximately 40% to 50% with the combination of pegylated interferon and ribavirin, to upwards of approximately 65% to 75% with the triple therapy regimen. Sustained virologic response is defined as an undetectable HCV viral load, typically measured 24 weeks after the completion of treatment, an end point that is associated with the long-term clearance of HCV, improved morbidity, and improved mortality.

In late 2013, the US Food and Drug Administration (FDA) approved sofosbuvir and simeprevir for the treatment of patients with HCV. Clinical trials with sofosbuvir suggested that 80% to 90% of patients should have undetectable virus levels 12 weeks after completing treatment. Clinical trials with simeprevir showed similar results, with almost 80% of patients showing undetectable HCV RNA levels after 12 weeks. Accordingly, in 2014, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America released treatment guidelines recommending sofosbuvir for all patients with HCV, except those with severe renal impairment. Two additional drugs were approved by the FDA in 2014 for the treatment of HCV infection—the combination of ledipasvir and sofosbuvir, and the combination of ombitasvir, paritaprevir, and ritonavir plus dasabuvir. In the short term, the utilization of older agents may continue at some level, because of individual patient needs and the cost of newer therapies, among other factors.

As health plans, pharmacy benefit managers, and other payers continue to define their clinical protocols in the rapidly changing environment of hepatitis C, and as RGT is used increasingly in other therapeutic areas, an evaluation of the adherence to RGT in the clinical management of HCV is necessary. This study measured adherence to the RGT guidelines and treatment futility rules for patients with chronic HCV based on the product labeling information for boceprevir and for telaprevir.

**Methods**

**Data Source**

The retrospective observational cohort study was conducted using the Humana research database, which included pharmacy claims, medical claims, laboratory claims, and enrollment data for more than 1.5 million fully insured commercial members, 1.9 million Medicare Advantage members, and 2.4 million Medicare Part D members from all 50 states at the time of the study. The study sample was restricted to members with complete medical and pharmacy claims in the fully insured commercial and Medicare Advantage coverage categories. Pharmacy claims data contained adjudication information for prescription medications, including drug name, dosage, quantity, days’ supply, and date of prescription fill. The medical claims data included up to 9 International Classification of Diseases, Ninth Revision, Clinical Modification codes for all inpatient and outpatient encounters. Medical claims data also included Current Procedural Terminology (CPT) codes, which were used in this study.
to identify HCV RNA viral load laboratory tests. Data from laboratory results were available for a subset of members and included Logical Observation Identifiers Names and Codes to identify laboratory results. Enrollment data contained information on demographics and coverage start and end dates. The study protocol was approved by Schulman Associates IRB’s Institutional Review Board under a minimal risk review.

**Sample Selection**

Patients aged ≥18 years to <90 years with a pharmacy claim for boceprevir or telaprevir were identified for the study sample. Age was assessed at the date of the first pharmacy claim for boceprevir or telaprevir. A medical diagnosis for hepatitis C was not required for inclusion, because boceprevir and telaprevir have no FDA-approved indications other than for hepatitis C. Patients were required to have 32 weeks of health plan enrollment after the first claim for boceprevir or telaprevir based on the recommended duration of therapy (Figure 1).

The date of the first pharmacy claim for boceprevir or telaprevir during the enrollment period was defined as the index date. The patients’ claims were observed for the period starting at the index date through 32 weeks after the index date, during which they were required to have continuous eligibility. The 32-week follow-up period allowed for the required HCV RNA laboratory monitoring to occur and for treatment patterns to be assessed.

**RGT Outcomes and Analyses**

RGT with boceprevir and telaprevir includes the monitoring of HCV RNA levels at routine intervals to determine how to proceed with drug therapy. Patients are deemed to be an early responder if their HCV RNA levels, which are measured fairly soon after initiating treatment, are undetectable. Early responders should have a shorter duration of therapy to prevent unnecessary drug exposure. On the contrary, patients with greater-than-expected levels of HCV RNA measured soon after initiating therapy, or later, are deemed to be nonresponders and should discontinue therapy according to the futility rules. Applying the futility rules reduces unnecessary drug exposure and minimizes the development of drug resistance for patients who have little chance of achieving a sustained virologic response.

**HCV RNA monitoring.** Adherence to the recommended HCV RNA monitoring was measured as the proportion of eligible patients who had an HCV RNA assay at each of the recommended time intervals of 8, 12, and 24 weeks for boceprevir, and 4, 12, and 24 weeks for telaprevir. For RGT, because some patients do not complete a full course of therapy, a given patient will require 1, 2, or 3 assays depending on his or her length of treatment. To account for this, adherence was measured as the number of patients who had an assay taken from the number of eligible patients at a given interval, where the number of eligible patients for each interval was determined by using the amount of prescription fills for each medication as a proxy.

HCV RNA assays were required to be on the guideline-specified date (based on the index date) or up to 21 days after that date to be classified as adherent. The 21-day buffer allowed for scheduling flexibility encountered in real-world clinical practice. The category I and category II CPT codes that were used to identify the HCV RNA assays included 3220F, 3265F, 87520, 87521, and 87522.

**Treatment futility rules.** An assessment of adherence to the futility rules was conducted among a subset of patients with laboratory results data and whose HCV RNA assays were drawn in the recommended time frame.
frames (as defined in the HCV RNA monitoring analysis). Adherence to futility rules was measured as the proportion of patients who correctly stopped therapy among all patients who had an HCV RNA result that indicated treatment futility at each monitoring interval. A patient was determined to have stopped therapy if there were no additional pharmacy claims for HCV therapy after the laboratory date where futility was determined. The Logical Observation Identifiers Names and Codes that were used to identify HCV RNA assay results included 5010-4, 5011-2, 5012-0, 11259-9, 38998-1, 48576-3, 51655-9, 53825-6, and 59052-1.

Results

Sample Characteristics
A total of 326 patients were included in the HCV RNA monitoring analysis, 65 receiving boceprevir and 261 receiving telaprevir; of these, 134 patients were included in the futility rules analysis, including 20 patients in the boceprevir group and 114 in the telaprevir group (Figure 2).

The study sample of 326 patients was primarily male (63.2%), insured by Medicare (66.5%), and treated by a gastroenterologist (52.4%). Table 1 lists the characteristics of the study population. These characteristics were similar in patients receiving boceprevir and in patients receiving telaprevir. Patient out-of-pocket (OOP) costs per prescription were higher in the telaprevir treatment group than in the boceprevir treatment group. The range of OOP costs in both groups was wide, because OOP costs vary by plan benefit design.

HCV RNA Monitoring
There were 1203 HCV RNA assays during the follow-up period among the 326 patients included in the study sample. The mean number of assays was 3.69, with a range of 0 to 26 assays per patient. In the individual patient-level analysis, 19 (29.2%) of the 65 patients in the boceprevir group and 84 (32.2%) of the 261 patients in the telaprevir group were adherent throughout their entire treatment period (data not shown). Adherence to HCV RNA monitoring was highest at the first recommended time interval for the boceprevir (66.2% at 8 weeks) and telaprevir (61.7% at 4 weeks) groups (Table 2). There was a downward trend in adherence at the second and third time intervals in both groups.

Treatment Futility Rules
Of the 134 patients eligible for this analysis, 20 met the futility rules for stopping therapy based on the HCV RNA assay results. Of those 20 patients, 11 (55%) stopped therapy in accordance with the treatment futility rules (Table 3). Therapy was continued in 9 people, despite meeting the futility rules. There was a directional trend in improved adherence to treatment futility rules over time.

Discussion
In this study, adherence to the RGT guidelines for boceprevir and telaprevir was suboptimal. A breach of these guidelines may contribute to unnecessary drug exposure and to the development of resistant hepatitis C variants. Specifically, we found that adherence to HCV RNA monitoring during the entire treatment period was 29.2% in the boceprevir group and 32.2% in the telapre-

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Table 1  Sample Characteristics of an HCV RNA Monitoring Analysis Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boceprevir N = 65</th>
<th>Telaprevir N = 261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, N (%)</td>
<td>40 (64.5)</td>
<td>166 (63.6)</td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>57.5 (8.0)</td>
<td>55.9 (7.5)</td>
</tr>
<tr>
<td>Insurance type, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>21 (32.3)</td>
<td>88 (33.7)</td>
</tr>
<tr>
<td>Medicare</td>
<td>44 (67.7)</td>
<td>173 (66.3)</td>
</tr>
<tr>
<td>Patient OOP cost per prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, $ (SD)</td>
<td>553 (704)</td>
<td>1296 (1336)</td>
</tr>
<tr>
<td>Range, $</td>
<td>0-3314</td>
<td>0-5073</td>
</tr>
<tr>
<td>Provider type, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>31 (47.7)</td>
<td>140 (53.6)</td>
</tr>
<tr>
<td>All other physician specialties</td>
<td>13 (20.0)</td>
<td>33 (12.6)</td>
</tr>
<tr>
<td>Nonphysician*</td>
<td>12 (18.5)</td>
<td>59 (22.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (13.8)</td>
<td>29 (11.1)</td>
</tr>
</tbody>
</table>

*Physician’s assistant, nurse practitioner, or pharmacist.

Table 2  HCV RNA Monitoring Results

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Eligible patients, N</th>
<th>Assays, N</th>
<th>Eligible patients adherent to HCV RNA monitoring guidelines, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (N = 65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 wks</td>
<td>65</td>
<td>43</td>
<td>66.2</td>
</tr>
<tr>
<td>12 wks</td>
<td>55</td>
<td>24</td>
<td>43.6</td>
</tr>
<tr>
<td>24 wks</td>
<td>40</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>Telaprevir (N = 261)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 wks</td>
<td>261</td>
<td>161</td>
<td>61.7</td>
</tr>
<tr>
<td>12 wks</td>
<td>205</td>
<td>120</td>
<td>58.5</td>
</tr>
<tr>
<td>24 wks</td>
<td>164</td>
<td>68</td>
<td>41.4</td>
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</table>

HCV RNA indicates hepatitis C virus ribonucleic acid.
Table 3  Treatment Futility Rule Results

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Futility rule</th>
<th>Patients with HCV RNA assay, N</th>
<th>Met futility rule, N (%)</th>
<th>Appropriately stopped therapy, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td>No futility rule</td>
<td>114</td>
<td>5 (25.0)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>12 wks</td>
<td>Stop treatment if HCV RNA is ≥100 IU/mL</td>
<td>20</td>
<td>3 (15.0)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>24 wks</td>
<td>Stop treatment if HCV RNA is detectable</td>
<td>12</td>
<td>1 (8.3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Telaprevir (N = 114)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 wks</td>
<td>Stop treatment if HCV RNA is &gt;1000 IU/mL</td>
<td>114</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>12 wks</td>
<td>Stop treatment if HCV RNA is &gt;1000 IU/mL</td>
<td>89</td>
<td>4 (4.5)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>24 wks</td>
<td>Stop treatment if HCV RNA is detectable</td>
<td>51</td>
<td>8 (15.7)</td>
<td>6 (75)</td>
</tr>
</tbody>
</table>

HCV RNA indicates hepatitis C virus ribonucleic acid.

There was a mean of 3.69 assays per patient, with a range of 0 to 26, indicating that patients are getting excess assays, and some patients may not be getting them within the recommended time frames. To our knowledge, the clinical implications on sustained virologic response or the financial impact of laboratory tests drawn outside of the recommended time frames have not been reported in the literature.

In addition, we identified 134 patients for the futility rules analysis, of which 20 (14.9%) met the stopping criteria based on HCV RNA laboratory values. The treatment failure rate of 14.9% was similar to the rates reported for boceprevir (8%-17%) and telaprevir (8%-13%) in clinical trials. Although the size of the sample in our study was small, 45% of the patients who met the futility rule continued therapy. Continuing treatment when the patient is not clearing the virus not only impacts needless risk to the patient, but it also contributes to an unnecessary cost to the patient and to unjustified costs to the healthcare system. To illustrate this point, if a patient were to fail treatment with boceprevir at week 8, but continue therapy for 36 weeks, at a wholesale acquisition cost of $19.90 per unit, the unnecessary costs of boceprevir alone would be nearly $47,000. This example estimate would vary based on a number of factors, including the length of treatment, the contracted drug price, and other treatment-related costs.

Adjusting therapy according to response is not a new concept; this paradigm has been used for several years in areas including anticoagulation, infectious disease, and heart failure. However, the concern of suboptimal adherence to RGT in clinical practice is increasingly relevant, because this approach is being used for specialty pharmacy therapeutics. For example, a phase 3 trial of response-guided neoadjuvant chemotherapy in early-stage breast cancer found a higher rate of disease-free survival (hazard ratio, 0.78; 95% confidence interval, 0.62-0.97) and an exploratory analysis trended toward improved overall survival compared with conventional therapy.

Similarly, response-guided induction therapy in pediatric acute myeloid leukemia has been shown to increase remission rates. In addition, a randomized phase 3 study showed early response using dose-intensive response-based chemotherapy and radiation in pediatric patients with intermediate-risk Hodgkin lymphoma.

Stopping therapy appropriately when futility rules are met is also important. Given the adverse clinical risks and economic consequences of extending treatment without a clinical benefit, all stakeholders in the healthcare ecosystem must collaborate to effectively implement RGT. One approach is for payers to modify prior authorization criteria to ensure compliance. Prior authorizations for drug therapy are frequently given for a year of treatment, but a prior authorization requiring documentation of assays and results during the year of treatment could result in better adherence to RGT, reducing drug exposure to the patient and saving costs. Because prior authorizations have time and financial impacts and are onerous on both the physician and the health plan, the administrative burden must be considered in the context of the potential benefit to the patient for any proposed utilization management tactics using RGT.

Limitations

The study population was derived from only one payer’s membership and, although the sample included commercial and Medicare Advantage members from all 50 states, the membership is concentrated in the Southeast and Midwest regions of the United States. Accordingly, our findings may not be reflective of the entire US population. Although the availability of laboratory data in the data set allowed for a sufficient cohort, the sample of patients who could be evaluated for adherence to futility rules was small, and further study should seek to validate the trends that were observed.

Although the results of this study are important for understanding adherence to RGT, the treatment landscape for HCV is rapidly evolving with the approval of new drugs and the October 2014 withdrawal of telaprevir from the market. Therefore, these findings have limited applicability in the present HCV practice environment.
To measure HCV RNA monitoring, we required that the assay be recorded on day 1 of the recommended time frame or within 21 days after. Our approach may have misclassified some laboratory values as non-adherent if those values occurred earlier than day 1 of the recommended time frame. The guidelines for the management of HCV do not clearly state the RGT criteria, even though the RGT criteria from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America are included in the package inserts of the respective drugs. The lack of specialty society guidelines may contribute to non-adherence with the recommendations.

Finally, we used prescription claims data to classify whether a patient had stopped therapy according to the futility rules. Filing a prescription claim does not definitively indicate that a patient consumed the medication, and our results should be interpreted in that context.

**Conclusion**

RGT is a well-established paradigm for drug therapy. In the patients with hepatitis C, however, the implementation of this approach was suboptimal in our study population. Our study is an important contribution to the literature, because there are few data sets containing laboratory results that are large enough to permit an assessment of adherence to futility rules in the management of HCV. Because this approach of guiding drug therapy based on individual patient response is being used increasingly in specialty pharmaceuticals, efforts to improve its uptake may enhance patient care and may also reduce unnecessary expenditures. All members of the patient care team, including payers, are responsible for the optimal implementation of RGT.

**Author Disclosure Statement**

Dr Harris and Dr Schwab reported no conflicts of interest; Dr Ward is a former employee of Humana and is currently an employee of GlaxoSmithKline.

**References**

19. Viekkra Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) [prescribing information]. North Chicago, IL: AbbVie, Inc; December 2014.
PATIENTS/PROVIDERS: The current estimated number of patients with hepatitis C virus (HCV) infection in the United States ranges from 3 million to 5 million, with an additional total of 185 million patients worldwide. In recent years, there has been a dramatic increase in the number of prescriptions for telaprevir and boceprevir, the 2 common anti-HCV agents approved in the past 5 years. The increasing cure rates for HCV have resulted in more physicians prescribing these drugs, and these therapies are leading to exceptionally good outcomes.

PAYERS: The costs for novel treatments for HCV infection, however, are being perceived as having a potentially dramatic impact on many health insurance plans, including public payers (Medicare and Medicaid) and private health plans. One component of the Affordable Care Act that has been implemented across the Medicare and Medicaid programs is the pay-for-performance model, which focuses on the outcomes of care as a factor in the reimbursable amounts by Medicare. When it comes to therapies for HCV, the costs of the new treatment regimens, even the new therapies approved in 2014, are lower than the total expenses that would be necessary using the older treatment approaches and low cure rates.

The type of analysis presented in this issue by Harris and colleagues, using response-guided therapy, is precisely what is now being called for to evaluate such expenditures, using HCV therapy as an example. According to the authors, the use of response-guided therapy improves clinical outcomes, reduces unnecessary drug exposure for the patient, and avoids unnecessary costs.

RESEARCHERS: The methods and analyses used by Harris and colleagues in this evaluation of response-guided therapy are exceptionally carried out. The use of this approach as appropriately utilized in this study is precisely the type of clinical tool needed to fully evaluate the treatment protocols and outcomes related to the new therapies for HCV infection.

The call by Harris and colleagues for the enhanced implementation of response-guided therapy is most appropriate and necessary at this point. Their findings, the authors note, highlight the need for the improved implementation of this approach in other therapeutic areas as well. This study and conclusions should serve as a template for similar studies across various disease states and health insurance companies: this type of study amplifies precisely why this therapeutic tool is needed.