Improvement in Treatment Adherence in Patients with Chronic Hepatitis C

Background: Adherence to pegylated interferon (PIFN) plus ribavirin (RBV), especially in the first 12 weeks, affects sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV). RibaPak® (RBP) requires fewer tablets than RBV.

Aim: To determine if simplifying the dosing regimen of RBV impacts outcomes.

Methods: Ninety-two patients on RBP >12 weeks were categorized as follows: Group A (n = 22): treatment experienced with IFN/PIFN and RBV, Group B (n = 49): treatment naïve switched to RBP after >12 weeks RBV, Group C (n = 21): treatment naïve on RBP. Outcomes were compared between RBP and RBV in Groups A and B. Group C was compared to Group D—a matched control group of RBV-treated patients.

Results: Patients preferred RBP. RBP was associated with improved patient compliance, less side effects, improved quality of life and a trend toward improved SVR.

Conclusions: RibaPak offers an attractive alternative to RBV.
ence to combination therapy is known to be a crucial factor in achieving early virologic response (EVR) and subsequently SVR. Studies have shown that adherence to RBV, especially in the first 12 weeks of therapy (to achieve EVR), may be more important than adherence to PIFN (6–8).

Improved adherence to therapy in diseases other than HCV has been shown to be influenced by reduction of medication-induced side effects as well as by diminished pill burden. In fact, in patients with chronic conditions such as HIV, hypertension, diabetes mellitus, epilepsy, and ulcerative colitis, it has been shown that the number and frequency of tablets ingested (pill burden) has a significant effect on compliance, quality of life (QOL) and/or outcome (9–12).

In an extensive review of the transplant literature, Laederach-Hofmann and colleagues found that simplicity of medication regimen was the single most reliable predictor of adherence to treatment among organ transplant recipients (13).

Many novel treatments aimed at improving SVR rate for HCV are currently under development, but it is unlikely that FDA approval will be granted for another two-to-three years. Furthermore, it is likely that PIFN plus RBV will continue to be a crucial component of HCV treatment. Thus, it is important to examine what improvements can be made to the current treatment regimen that may optimize therapy.

RibaPak® (Three Rivers Pharmaceuticals, Cranberry Township, PA) (RBP) is a 400 mg and/or 600 mg RBV tablet that requires up to 66% fewer tablets than RBV (200 mg). RibaPak is available in a unit dose blister pack compared with traditional bottled RBV tablet or capsule. This study was undertaken to determine if simplifying the dosing regimen of RBV has an impact on adherence, AEs, and QOL of patients with HCV on combination therapy. While this study was not specifically designed to evaluate the efficacy of RibaPak versus RBV, SVR data were also assessed.

METHODS

Study Participants

From May 2006 to November 2006, 107 patients were identified who were on treatment with RibaPak and PIFN. Ninety-two patients met the following inclusion criteria and were entered into the study: adults (>18 years), chronic hepatitis C diagnosed by HCV RNA and liver biopsy, compensated chronic HCV—i.e., normal prothrombin time, serum albumin and bilirubin levels (unless due to non-hepatitis factors), no history of bleeding esophageal varices, ascites, or hepatic encephalopathy, had received treatment with pegylated interferon alpha 2b + RibaPak for >12 weeks at study enrollment, and complete data for evaluation and comparison AE’s, concomitant medications, pill count, QOL data. Patients were excluded from the study if one or more of the following were present: positive HIV or HBsAg serology, severe psychiatric disorder, history of thalassemia or other hemoglobinopathies, chronic liver disease other than hepatitis C, organ or bone marrow transplant, history of alcoholism or drug addiction within one year of study enrollment.

Study Design and Treatment Groups

This was a single-center, observational study comparing the incidence of AEs, treatment preference, QOL, treatment adherence, concomitant medication use, and SVR in patients receiving treatment for HCV with RBV and PIFN versus RibaPak and PIFN, for the initial 12 weeks of combination therapy. Patients were categorized into four cohorts as follows: (Figure 1) Group A (“treatment experienced”) were patients being treated with PIFN plus RibaPak >12 weeks who had previously received treatment with PIFN or IFN plus RBV but had either relapsed, failed to respond to treatment, or had discontinued treatment early due to AEs or noncompliance. Group B (“treatment naïve switch”) were patients who were switched to PIFN plus RibaPak after being treated with PIFN plus RBV for >12 weeks who had previously received treatment with PIFN or IFN plus RBV but had either relapsed, failed to respond to treatment, or had discontinued treatment early due to AEs or noncompliance. Group B (“treatment naïve switch”) were patients who were switched to PIFN plus RibaPak after being treated with PIFN plus RBV for >12 weeks. Groups A and B were evaluated at week 4, 8, and 12 for AEs, drug preference, QOL, treatment adherence, and concomitant medication use. Group C (“treatment naïve”) were patients who were treated with PIFN plus RibaPak for >12 weeks. Group C was evaluated every four weeks for the initial 12 weeks of combination treatment for AE’s, adherence, and concomitant medication use and comparisons were made with group D a consecutive matched control group of naïve patients treated with PIFN plus...
RBV ≥12 weeks. Patients in Group D were selected for the study based on matching patients in Group C as to fibrosis score, genotype, viral load (high versus low), race, and gender. All four cohorts were evaluated for SVR on an intention-to-treat (ITT) basis. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was supported by an unrestricted educational grant from Three Rivers Pharmaceuticals.

Outcomes
Adverse events, drug preference, QOL, adherence, and concomitant medication data were collected at treatment weeks 4, 8 and 12 as above. Virological data were collected at the end of treatment [(EOT)—treatment week 24 or 48] and 24 weeks after treatment discontinuation (SVR).

Adverse Events
Adverse events were collected from the patient’s medical record and/or physician/patient interview during the RBV and RibaPak treatment periods.

Patient Preference
Patients in Groups A and B were asked whether they preferred RibaPak, preferred RBV or had no preference. Patients who stated a preference were also asked the reason why they preferred one treatment over the other.

Quality of Life
Quality of life was assessed using a modified version of the Short Form 36 (SF-36). The SF-36 is a general QOL assessment survey with 36 questions that make up eight sub-scales (physical function, physical role limitation, bodily pain, general health, vitality, social functioning, emotional role limitation, and mental health). The SF-36 is widely used and has been validated in diverse disease states including patients with advanced liver disease (14–18). For the purposes of this study, a composite of the above sub-scales was used and comparisons were made between RBV and RibaPak treatment periods within Groups A and B.

Adherence
Patients were instructed to bring in used and unused drugs at each visit. Capsules/tablets of RBV and tablets of RibaPak from blister packs were counted and recorded every four weeks for 12 weeks to assess patient compliance. In instances in which patients did not bring in their medication, a verbal count from the patient was accepted.

Concomitant Medications
Data on concomitant medication use were obtained from the patients’ medical records in addition to patient/physician interviews. Necessity for concomitant medication use was compared between patients taking RBV versus RibaPak—in groups A and B, and was compared between patients taking RibaPak in Group C and patients taking RBV in Group D.
Virological Response
End of treatment response and SVR data were assessed using Heptimax (HCV RNA <5 IU/mL) (Quest diagnostics). All groups were evaluated for SVR on an intention-to-treat (ITT) basis.

Statistical Analysis
Statistical analysis was performed using Student’s t-test or Chi Square test as appropriate.

RESULTS
Sample Population Demographics
One hundred seven patients were identified who were on treatment with RibaPak and PIFN. A total of 92 patients met the inclusion and exclusion criteria and were enrolled in the study. Group A, treatment experienced, included 22 patients (n = 8 relapses, n = 5 non-responders, n = 9 early terminations due to AEs or noncompliance), Group B had 49 naïve patients who were switched to RibaPak following ≥12 weeks of RBV, and Groups C (started treatment with RibaPak) and D (matched control started treatment with RBV) had 21 patients each. Mean age was 49 ± 6.2 years. The majority of patients were Caucasian (83.7%, 77/92), 8.7% (8/92) were African American and 7.6% (7/92) were Hispanic. Sixty-two percent (57/92) were male and 38% (35/92) were female. The majority were genotype G1 (90.2%, 83/92), 5.4% (5/92) were G2 and 4.3% (4/92) were genotype G3. Fifty-nine percent of patients (54/92) had a high viral load (HCV RNA >800,000 IU/mL). Liver histology was as follows: 27.2% (25/92) were fibrosis score F1, 40.2% (37/92) were F2, 19.6% (18/92) were F3 and 13.0% (12/92) had cirrhosis (F4) (Table 1).

There were no significant differences in demographics between any cohorts.

Adverse Events
Group A (Treatment experienced)
Thirty-two percent (7/22) of patients in Group A reported less AEs over the 12 week period on RibaPak compared to prior treatment with RBV. Nausea was decreased in 31.8% (7/22) of patients, LOA in 27.3% (6/22), dyspepsia in 27.3% (6/22), weight loss (> 5 lbs) in 22.7% (5/22), diarrhea in 9.1% (2/22), and headache in 4.5% (1/22) of patients (Figure 2).

Group B (Treatment naïve switch)
Thirty-five percent (17/49) of patients in Group B reported less AEs during 12 weeks of RibaPak treatment compared to the previous 12-week treatment with RBV.

Nausea was decreased in 26.5% (13/49) of patients, LOA in 16.3% (8/49), dyspepsia in 28.6% (14/49), weight loss (>5 lbs) in 20.4% (10/49), diarrhea in 6.1% (3/49), and fatigue in 2.0% (1/49) of patients (Figure 3).
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Group C (Treatment naïve on RibaPak) & Group D (control group—Treatment naïve on RBV)

 Patients taking RibaPak reported less gastrointestinal AEs compared to patients taking RBV over the compared 12 week treatment period. Thirty-three percent (7/21) of patients taking RBV reported weight loss (>5 lbs) compared to 14.3% (3/21) of patients taking RibaPak, 28.6% (6/21) of patients taking RBV reported nausea compared to 9.5% (2/21) of patients taking RibaPak, 28.6% (6/21) of patients taking RBV reported LOA compared to 14.3% (3/21) of patients taking RibaPak, 23.8% (5/21) of patients taking RBV reported dyspepsia compared to 9.5% (2/21) of patients taking RibaPak, and 14.3% (3/21) of patients taking RBV reported diarrhea compared to 4.8% (1/21) of patients taking RibaPak (Figure 4).

Quality of Life Composite Score

Groups A and B

 Quality of life scores improved in 63.6% (14/22) of patients in Group A following treatment with RibaPak compared to prior treatment with RBV (RBV n = 0; RBP n = 14; no difference n = 8). Quality of life scores also improved in 75.5% (37/49) of patients in Group B following a treatment switch from RBV to RibaPak (RBP n = 37; no difference n = 12).

Adherence

 Treatment with RibaPak was associated with an improvement in adherence to treatment in all study groups. Over the 12 week treatment period with RibaPak, patients in Group A missed a total of 3 pills (corresponding to 1600 mg), versus 27 pills (5400 mg), over a 12 week treatment period with RBV. In Group B, patients missed none of their prescribed pills during the 12 week treatment period with RibaPak, versus missing 11 pills (2200 mg) during the 12 week treatment period with RBV. In Groups C and D, only one pill (600 mg) was missed in the group of patients taking RibaPak compared to 5 pills (1000 mg) in the control group of patients taking RBV (Table 2).

Patient Preference for RibaPak vs. RBV

 Sixty-eight percent (15/22) of patients in Group A and 81.6% (40/49) of patients in Group B reported a preference for RibaPak over RBV; 31.8% (7/22) of
patients in Group A and 18.4% (9/49) of patients in Group B reported no preference. No patients in Group A or Group B reported a preference for RBV over RibaPak (Figure 5).

Diminished AEs, improved QOL and/or simplification of drug regimen both pill burden and/or blister pack convenience, were reported as being the reasons patients preferred RibaPak to RBV.

### Table 2
**Number of pills missed for patients taking RibaPak® vs. ribavirin**

<table>
<thead>
<tr>
<th></th>
<th>RBV</th>
<th>RibaPak®</th>
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<tbody>
<tr>
<td>Group A (“Treatment Experienced,” n = 22)</td>
<td>27 (5,400 mg)</td>
<td>3 (1,600 mg)</td>
</tr>
<tr>
<td>Group B (“Treatment Naïve Switch,” n = 49)</td>
<td>11 (2,200 mg)</td>
<td>0</td>
</tr>
<tr>
<td>Group C (“Treatment Naïve RibaPak®,” n = 21)</td>
<td>N/A</td>
<td>1 (600 mg)</td>
</tr>
<tr>
<td>Group D (“Treatment Naïve Ribavirin,” n = 21)</td>
<td>5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Figure 4. Percent of RibaPak® and RBV patients experiencing specific adverse events (Group C: Treatment naïve on RibaPak) and Group D (control group—Treatment naïve on RBV)

Figure 5. Percent of patients in Groups A and B stating a preference for RibaPak®, RBV, or no preference (Group A: Treatment experience, n = 22, Group B: Treatment naïve switch, n = 49)
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Concomitant Medications
Patients in Groups A and B required less concomitant medication use of metoclopramide, loperamide, proton pump inhibitors, dronabinol, antacids and H$_2$ blockers during treatment with RibaPak compared to treatment with RBV. Similarly, patients treated with RibaPak in Group C required less of the same concomitant medications compared to patients on RBV in Group D. No concomitant medication was required more frequently in patients taking RibaPak compared to RBV in any group.

Virological Response
Early virological response was achieved in 73.9% (68/92) of patients overall. Sustained virological response was achieved in 64.1% (59/92) of all patients (continued on page 40)

Table 3
Active ingredients in RibaPak vs. ribavirin

<table>
<thead>
<tr>
<th>Company</th>
<th>Brand Name</th>
<th>Inactive Ingredients</th>
</tr>
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<tbody>
<tr>
<td>Three Rivers Pharmaceuticals</td>
<td>Ribasphere®</td>
<td>Microcrystalline cellulose, lactose monohydrate, croscarmellose, sodium, povidone K29-33, magnesium stearate, and purified water. The coating of the 400 and 600 mg tablet contains partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, t alc, FD&amp;C blue #1 [brilliant blue FCF aluminum lake], and carnauba wax.</td>
</tr>
<tr>
<td></td>
<td>RibaPak®</td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Copegus®</td>
<td>The core of the tablet contains cornstarch, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The coating of the tablet contains ethyl cellulose (200 mg tablet only), hydroxypropylmethyl cellulose, red iron oxide, talc, titanium dioxide, triacetin, and yellow iron oxide.</td>
</tr>
<tr>
<td>Zydus Pharmaceuticals</td>
<td>Ribavirin</td>
<td>Crospovidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, silicon dioxide, talc and titanium dioxide.</td>
</tr>
<tr>
<td>Schering</td>
<td>Rebetol®</td>
<td>Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&amp;C Blue #2 aluminum lake.</td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries Ltd</td>
<td>Ribavirin</td>
<td>The core of the tablet contains cornstarch, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The coating of the tablet contains ethyl cellulose (200 mg tablet only), hydroxypropylmethyl cellulose, red iron oxide, talc, titanium dioxide, triacetin, and yellow iron oxide.</td>
</tr>
<tr>
<td>Sandoz</td>
<td>Ribavirin</td>
<td>Croscarmellose sodium, FD&amp;C Blue #2 aluminum lake, gelatin, hypromellose, magnesium stearate, mannitol, povidone, propylene glycol, shellac, titanium dioxide.</td>
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Figure 6. Percent of patients achieving SVR, overall and within genotype 1

with a relapse rate of 9.8% (Figure 6). When evaluated by genotype, SVR was achieved in 61.4% (51/83) of genotype 1 patients and in 88.9% (8/9) of patients with genotype 2/3.

Group A (Treatment experienced)
In Group A, SVR was achieved in 27.3% (6/22) of patients following treatment with RibaPak, and in 23.8% (5/21) of patients with genotype 1 (Figure 6). The one patient with genotype 2/3 in Group A achieved SVR.

Group B (Treatment naïve switch)
In Group B, SVR was achieved in 55.1% (27/49) of patients overall, and in 55.3% (26/47) of patients with genotype 1 (Figure 6). One of the two patients with genotype 2/3 in Group B achieved SVR.

Group C (Treatment naïve RibaPak) and D (Treatment naïve RBV)
Sustained virological response was achieved in 66.7% (14/21) of patients treated with RibaPak in Group C compared to 57.1% (12/21) of patients treated with RBV in Group D. When broken down into genotype, SVR was achieved by 61.1% (11/18) of genotype 1 RibaPak-treated patients in Group C and 50.0% (9/18) of genotype 1 RBV-treated patients in Group D (Figure 6). All three genotype 2/3 patients in both the RibaPak and RBV groups achieved SVR.

DISCUSSION
This study demonstrates an improvement in adherence to therapy, a decrease in AEs and concomitant medication use, as well as an improvement in QOL in patients with chronic hepatitis C treated with PIFN plus RibaPak compared with PIFN plus RBV. Patients also reported a preference for RibaPak versus RBV generally due to diminished AEs primarily gastrointestinal (GI) in nature, improved QOL, and simplification of drug regimen. In addition, a trend toward a greater proportion of patients achieving SVR was observed in patients treated with RibaPak versus RBV.

RibaPak requires up to 66% fewer tablets than RBV. Thus, the diminished pill burden associated with RibaPak was likely a significant factor in the improved adherence to therapy observed for RibaPak versus RBV. Adherence to therapy was measured using a combination of both pill count and patient self-report. Both methods of adherence monitoring may overestimate compliance behavior (19). However, the
results from the present study are consistent with data from other patient populations in which decreased pill burden has been associated with improved compliance (9-13). Some patients in this study felt that the use of RibaPak blister packs also supported patient compliance. This is similar to findings of a study conducted at the Walter Reed Army Medical Center which concluded that adherence to medication improved from 61% in patients using traditional bottled product to 97.6% in patients using blistered card product (20).

In addition to improved treatment adherence, patients on RibaPak experienced less AEs than patients on RBV. The most significant decrease was observed for GI-related AEs such as nausea, LOA, dyspepsia, and diarrhea. Drug-associated AEs are an important cause of dosing decreases and treatment discontinuation, and lack of adequate ribavirin dosing is an important cause of treatment failure. Therefore, the decrease in AEs observed for RibaPak has implications to treatment adherence and ultimately, clinical response. The decrease in AEs associated with RibaPak is most likely due to pill burden. Whether the diminished AEs associated with RibaPak observed in this study were due to a difference in inactive ingredients requires further investigation. However, a preliminary comparison of the inactive ingredients as noted in Table 3 does not support major differences.

Patients with HCV often have reduced QOL while on treatment that is typically most pronounced during the first four-to-12 weeks of therapy (19,21,22). In this study, patients reported an improved QOL while taking RibaPak versus RBV. This improvement may be due to a decrease in side effects experienced while on RibaPak, and/or the diminished pill burden of RibaPak. In either case, any variable which impacts positively on QOL will likely prove to be an important parameter to maintaining treatment adherence.

Due to the observational nature of this study, we are limited in making causal inferences regarding the effect of RibaPak on SVR. However, there was a trend toward improved EVR and SVR rates in patients taking RibaPak versus RBV. This improvement may be due to a decrease in side effects experienced while on RibaPak, and/or the diminished pill burden of RibaPak. In either case, any variable which impacts positively on QOL will likely prove to be an important parameter to maintaining treatment adherence.

In conclusion, RibaPak blister packs offer an attractive alternative to traditional RBV bottled pills. Patients prefer RibaPak compared to RBV due to decreased number of pills, convenience of the blister pack administration, diminished side effects (primarily GI) and improved QOL. RibaPak is associated with improved patient compliance compared to RBV. This has the potential to avoid wasted drug costs and reduce future comorbidity that is associated with significant health care expense. As the future of HCV treatment will likely involve the addition of a third drug (such as a polymerase or protease inhibitor), simplification of the treatment regimen by a reduction in the number of pills may be crucial to treatment success. Based on the beneficial effects of RibaPak observed in this study, a multi-center, prospective, observational registry, known as the ADHERE registry, capturing data on
compliance with RibaPak versus RBV in over 500 patients to date with HCV in the United States, is currently ongoing.

References

20. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA, 2006;296:2563-2571.