Impact of Specialty Pharmacy on Telaprevir-Containing 3-Drug Hepatitis C Regimen Persistence

Rochelle R. Henderson, PhD, MPA; Jay Visaria, PhD, MPH; Gail G. Bridges, PharmD; Mary Dorholt, PharmD; Rebecca J. Levin, MS; and Sharon Glave Frazee, PhD, MPH

ABSTRACT

BACKGROUND: Although the recommended treatment of hepatitis C continues to evolve as newer and more effective medications are made available, hepatitis C drug regimens consisting of a 3-drug combination of a protease inhibitor, pegylated interferon, and ribavirin were recommended by the American Association for the Study of Liver Diseases for the HCV genotype I beginning in 2011. Although more effective than the earlier standard of care, these regimens have complex dosing schedules, prolonged duration, and deleterious side effects. It has been shown that patients tend to discontinue these regimens prematurely. Specialty pharmacies offer specialized care management programs to hepatitis C patients, consisting of such services as regularly scheduled patient counseling, assessing regimen appropriateness, monitoring treatment progress, scheduling refill reminders, and coordinating patient care with prescribers. The use of specialty pharmacies by hepatitis C patients may improve persistence on the 3-drug hepatitis C regimens.

OBJECTIVE: To examine the association of pharmacy dispensing channel (specialty pharmacy or retail pharmacy) and hepatitis C regimen persistence among patients on a 3-drug hepatitis C regimen containing telaprevir, a widely used hepatitis C protease inhibitor.

METHODS: A retrospective, observational study was conducted using pharmacy claims data from a national pharmacy benefits manager for the period July 2011 to June 2013. Continuously eligible patients who started a new 3-drug regimen containing telaprevir were included in the study and followed for up to 12 months after the index hepatitis C claim. The study outcome was persistence to the 3-drug regimen at treatment week 24 (day 168), representing the completion of an important milestone in the regimen. Patients were defined as persistent if they filled 84 days' supply of telaprevir and 168 days' supply of pegylated interferon and ribavirin each, as required by the regimen protocol. Multivariate logistic regression was used to evaluate the association between dispensing channel and persistence, controlling for differences in demographics, medication burden, out-of-pocket spend per 30-day adjusted hepatitis C prescription, and average days' supply per unadjusted hepatitis C prescription.

RESULTS: The final study sample consisted of 1,475 patients—1,182 in the specialty pharmacy group and 293 in the retail pharmacy group. A significantly greater proportion of patients were persistent to the 3-drug hepatitis C regimen containing telaprevir in specialty pharmacy, compared with retail pharmacy (56.0% vs. 39.9%, $P<0.001$). After multivariate adjustment, patients in the specialty pharmacy group had 1.89 times greater odds of being persistent to 3-drug hepatitis C regimens containing telaprevir compared with patients in the retail group (95% CI=1.44-2.48).

CONCLUSIONS: Patients who used a specialty pharmacy offering refill reminders, care management, and care coordination with prescribers were significantly more likely to be persistent to 3-drug hepatitis C regimens, compared with patients using a retail pharmacy.

J Manag Care Pharm. 2014;20(12):1227-34

What is already known about this subject

- Three-drug treatment regimens consisting of pegylated interferon, ribavirin, and a protease inhibitor were recommended in 2011 by the American Association for the Study of Liver Diseases for HCV genotype I hepatitis C treatment. These 3-drug regimens demonstrated higher cure rates compared with the previous standard of care, a 2-drug combination of pegylated interferon and ribavirin.
- Patients on multidrug hepatitis C regimens are at high risk of prematurely discontinuing treatment. Patients on the 3-drug regimens may be at greater risk for discontinuation than those on 2-drug regimens due to more complex dosing schedules, variable duration of treatment, and additional adverse events resulting from the addition of a third drug.
- Specialty pharmacies have been successful at improving regimen adherence and reducing the number of dose reductions in patients on 2-drug hepatitis C regimens.

What this study adds

- This study provides evidence from a real-life practice setting that the benefits of using a specialty pharmacy, already established in studies investigating patients on 2-drug regimens, also extend to patients on 3-drug regimens.
- Patients using specialty pharmacy were significantly more likely to be persistent to a 3-drug hepatitis C regimen containing a protease inhibitor compared with those using retail pharmacies.
- Use of specialty pharmacies may be an even more attractive option, as new hepatitis C agents, which cost approximately $84,000 for the 12-week treatment regimen, enter the market, and payers and plan sponsors are faced with balancing improving outcomes from their hepatitis C patients and the significant treatment costs.

Hepatitis C virus (HCV) infection affects 1.3% of all Americans, with an estimated 2.3-2.7 million developing chronic hepatitis C infection and 68% of whom have HCV genotype 1.[1,2] Although the prevalence of hepatitis C has been declining since 1991, the number of patients living with hepatitis C-related complications, such as advanced fibrosis, liver cirrhosis, and hepatocellular carcinoma, are projected to increase in the coming decade.[3] In May 2011,

a significant advancement in the treatment of genotype I hepatitis C occurred with the introduction of 2 protease inhibitor (PI) medications: telaprevir and boceprevir.[4,5] These PI medications were used in addition to traditional pegylated interferon and ribavirin to provide a 3-drug combination treatment regimen.[4-9] Studies had shown that treatment with the 3-drug regimen resulted in shorter average duration of treatment and significantly higher rates of sustained viral response (SVR) in HCV genotype I patients compared with the earlier standard of care: a 2-drug combination pegylated interferon and ribavirin.[6,7] Achievement of SVR is an important clinical outcome for hepatitis C and has been associated with a lower risk of developing long-term complications, such as cirrhosis and hepatocellular carcinoma,[10] which results in lower health care utilization and reduced medical costs.[11] The availability of newer and more effective medications has resulted in the American Association for the Study of Liver Diseases (AASLD) modifying its guidance to include the daily sofosbuvir.[12]

Although efficacy had improved with the 3-drug regimens, research suggested that persistence remained a challenge with the 3-drug and 2-drug regimens. A review of 13 studies examining 2-drug hepatitis C regimens indicated that treatment regimen completion rates were suboptimal, with 5%-50% of patients failing to take 80% or more prescribed doses.[13] Therefore, the addition of a PI to the 2-drug regimen could have exacerbated the risk for nonpersistence with the addition of a third drug, as compared with the earlier 2-drug regimens. The variable duration of treatment with 3-drug regimens also contributes to regimen complexity, a known barrier to optimal adherence.[9] Treatment duration for the 3-drug regimens must be individualized for each patient and depends on several factors, including the patient's treatment history of hepatitis C, the extent to which hepatitis C infection responded to earlier treatment, and the viral response to the 3-drug regimen.[14]

Another roadblock to persistence can come in the form of regimen intolerance. Between 10%-21% of patients on 3-drug regimens have been reported to discontinue treatment due to adverse events such as fatigue and depression.[9] In order to maximize the likelihood of successfully completing the 3-drug regimens, patients require close clinical monitoring and coordination between the prescriber, pharmacist, and patient throughout the course of therapy.[7,9] Even with the newer HCV genotype I therapies, individualized monitoring and ongoing patient evaluation play a role in ensuring regimen tolerance, optimizing adherence, and minimizing waste.

Hepatitis C patients face many challenges in managing their treatment, including complex dosing regimens, coordination with physicians' offices for timely follow-up appointments, and coping with uncomfortable adverse effects. Patients also require training to use self-injectable pegylated interferons. While retail and other pharmacies continue to dispense these medications, specialty pharmacies offer specialized care management programs for patients using hepatitis C medications and provide several services targeted at optimizing outcomes for hepatitis C patients. Trained pharmacists and nurses specializing in hepatitis C provide counseling on medication usage, as well as education on medication self-administration, managing potential side effects, and responding to adverse drug reactions. Scheduled outreach calls are made to monitor patients' medication adherence, provide laboratory follow-up reminders, and evaluate hepatitis C-related quality of life. Results from viral response tests are monitored closely throughout the course of treatment by a pharmacist with specialized training on the treatment of hepatitis C to ensure that treatment duration is appropriate based on response-guided treatment algorithms. The pharmacy can also coordinate with the prescribing physician to ensure that appropriate medications are selected for each patient based on patient genotype, comorbidities, and treatment history. Specialty pharmacies can also intervene to stop therapy when further treatment is considered futile according to evidence-based prescribing guidelines, protecting patients from unnecessary drug exposure with potentially harmful side effects and ensuring efficient use of medications for payors.[7,9]

Evidence from previous studies have demonstrated that specialty pharmacies have been successful at improving medication adherence to 2-drug hepatitis C regimens and reducing the number of dose reductions required in hepatitis C patients.[15,16] As new hepatitis C agents (i.e., sofosbuvir and simeprevir), which cost approximately $84,000 for the 12-week treatment regimen, enter the market, payers and plan sponsors are faced with balancing the improving outcomes from their hepatitis C patients and the significant treatment costs. Thus, the use of specialty pharmacy may be an even more attractive option to maximize the likelihood that patients successfully complete therapy.

The objective of this analysis was to compare the likelihood of completing a 3-drug hepatitis C regimen containing telaprevir between patients using a specialty pharmacy offering a disease-specific care management program and those using a retail pharmacy. This analysis focused on the use of 3-drug regimens containing telaprevir, which accounted for over 80% of patients initiating 3-drug regimens at the time of this analysis.[8] Patients on 3-drug regimens using boceprevir were excluded, since only 103 patients were eligible for inclusion in the retail pharmacy group. Due to separate prescribing guidelines for telaprevir and boceprevir, patients using these drugs could not be combined for a pooled analysis. As expected, however, the most recent change in guidelines has shifted patient care from the 3-drug regimen containing telaprevir to the multidrug regimen containing simeprevir or sofosbuvir.

Methods

Data Source and Patient Selection

A claims-based, retrospective, observational study was conducted using prescription claims and eligibility data from a

large national pharmacy benefit management (PBM) company database housing prescription claims for patients for whom the PBM serves as the network claims processor. The PBM also operates an independent specialty pharmacy that serves patients across the United States. Thus, patients in the study could obtain their hepatitis C medications from the PBM-operated specialty pharmacy, external specialty pharmacies, home-delivery pharmacies, or retail pharmacies. Patients who used more than 1 dispensing channel to fill their hepatitis C medications were excluded from the analysis, since these patients did not have the opportunity to take advantage of all the possible care management interventions offered by a single dispensing channel throughout the course of therapy. Claims for the period from July 1, 2011, to June 30, 2013, were used in this analysis. Patients were selected if they started a new 3-drug regimen consisting of pegylated interferon, ribavirin, and telaprevir between January 1, 2012, and June 30, 2012. At a minimum, patients were required to fill at least 1 claim for telaprevir, pegylated interferon, and ribavirin during the follow-up period to be included in the study. A new start on the regimen was defined by a gap of at least 180 days between the index claim of the 3-drug regimen and any previous claim for a hepatitis C medication. Hepatitis C medications were identified based on the National Drug Code number (for a list of drugs used, see the Appendix, available in the online article). Patients were followed for up to 365 days after the index hepatitis C claim. All study patients were continuously eligible for pharmacy benefits for at least 180 days before and 365 days after the index hepatitis C claim. Patients were assigned to study groups based on whether the patient used the PBM-operated specialty pharmacy or retail pharmacies to fill their hepatitis C prescriptions.

Study Outcome

Persistence to medication is typically measured at a fixed time after therapy initiation, usually after a predetermined fixed interval or at the end of the follow-up period.[17] However, the duration of therapy for 3-drug regimens containing telaprevir is not fixed. The optimum duration of treatment is determined on an individual basis throughout the course of therapy based on the response of the hepatitis C virus to treatment at predetermined intervals. The optimum duration of treatment with telaprevir may vary between 24 or 48 weeks. Guidelines recommend that HCV genotype I patients be initiated on concurrent triple-therapy with telaprevir, pegylated interferon, and ribavirin.[18] All patients who show evidence of responding to treatment (HCV ribonucleic acid [RNA] undetectable or < 1,000 international units per milliliter [IU/mL] at treatment weeks 4 and 12) should continue concurrent triple-therapy until treatment week 12 and then continue treatment with pegylated interferon and ribavirin from treatment week 12 to treatment week 24. Further treatment beyond week 24 may be required for some patients depending on a number of factors, such as cirrhotic status, response to current treatment regimen, and outcomes from previous treatment (e.g., null or partial responder).[9] Thus, completing the regimen through week 24 is a treatment milestone common to all patients using 3-drug regimens containing telaprevir. For this study, patients were defined as persistent at week 24 of therapy if they filled 84 days' supply (12 weeks) of telaprevir, 168 days' supply (24 weeks) of pegylated interferon, and 168 days' supply (24 weeks) of ribavirin.

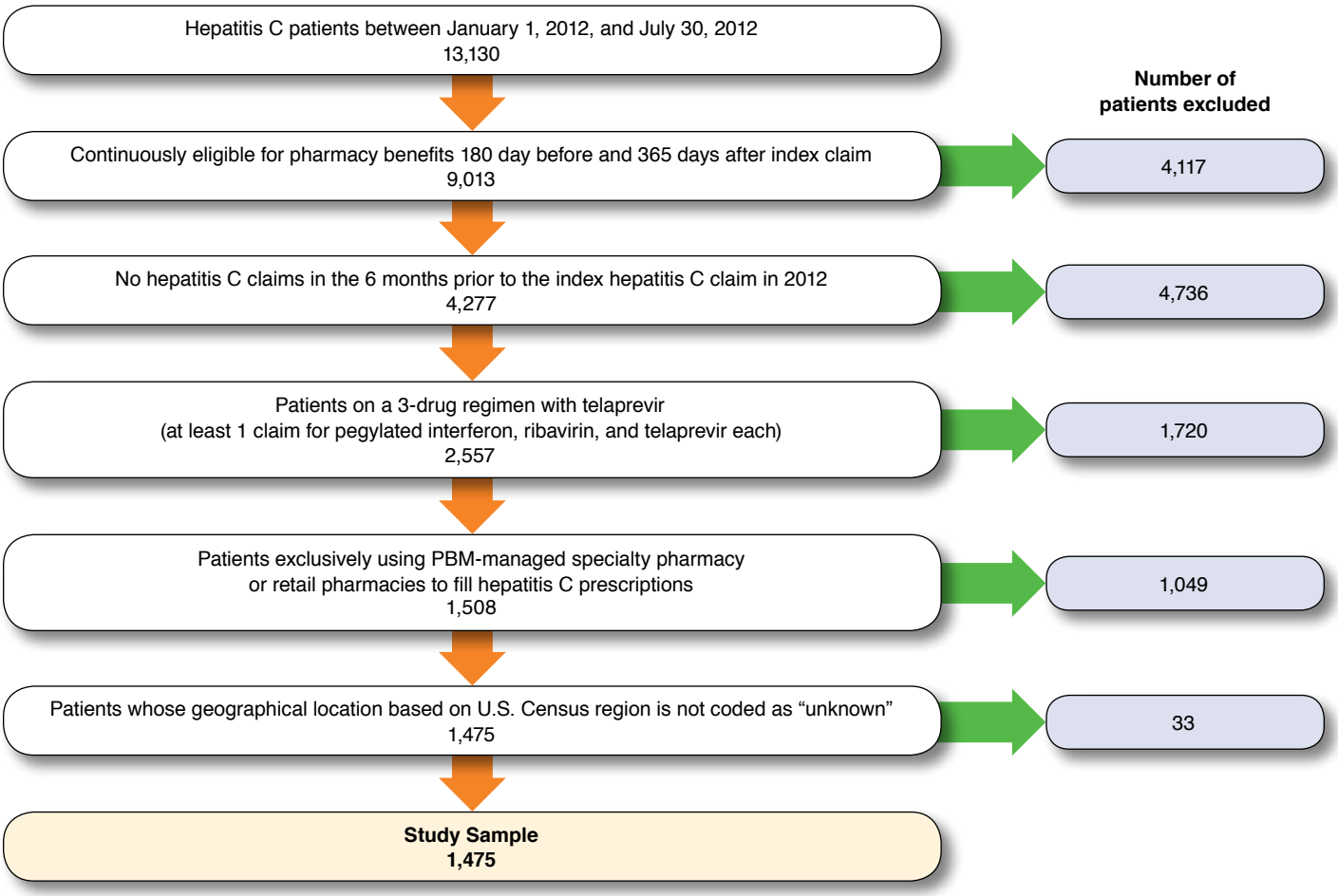
Statistical Analysis

Unadjusted differences between the retail and specialty pharmacy groups were evaluated using t-tests for continuous variables and chi-squared tests for categorical variables (alpha set a priori to 0.05). A multivariate logistic regression model was created with regimen persistence as the dichotomous dependent variable (1 = persistent at week 24 of therapy, 0 = not persistent), pharmacy type as the primary predictor (specialty or retail), and other covariates. Days persistent to the 3-drug regimen were calculated as the number of days between therapy initiation and the first instance of discontinuation of any of the 3 drugs in the regimen. Differences in days persistent to therapy between specialty pharmacy and retail pharmacy were compared using Kaplan Meier survival analysis and a log-rank test to compare the 2 survival curves. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Factors known to confound the relationship between persistence and channel were identified based on a literature review. Covariates for these factors or their proxies were generated from the pharmacy claims data and controlled in the multivariate analysis. Demographic confounders included patient age in 2012, patient gender, and U.S. region where the patient resided in 2012, based on the U.S. Census regional classification of states.[19] Patient out-of-pocket payment was defined as the average of the patient-paid amount (sum of copayment and deductible) per 30 days' supply of hepatitis C medication filled during the follow-up period.[15] The count of unique 2-digit Generic Product Indicator (GPI) codes observed in the patient's pharmacy claims record during the follow-up period was used as a proxy for patient medication burden.[15] Days of supply per unadjusted hepatitis C prescription was computed by dividing the total number of days' supply of hepatitis C medication filled during follow-up by the number of unadjusted hepatitis C prescriptions filled and was also included in the model as a covariate.[20]

Sensitivity analyses were conducted evaluating the impact of modifying the study definition of persistence (Table 3). In the main analysis, patients were required to have medication on hand for 100% of the days in the follow-up period in order to be defined as persistent. In the first sensitivity analysis, assuming 90% of days of supply filled to be adequate, patients were defined as persistent if they filled 152 days of pegylated interferon and ribavirin and 76 days of telaprevir. In the

FIGURE 1 Selection Algorithm and Count of Patients Included in a Patient Cohort of Hepatitis C Patients Between July 1, 2011, and December 31, 2013, in PBM Claims Data



PBM = pharmacy benefit management company.

second sensitivity analysis, assuming 80% of the days of supply at week 24 to be adequate, patients were defined as persistent if they filled 135 days of pegylated interferon and ribavirin and 68 days of telaprevir. Both sensitivity analyses were also repeated without relaxing the days of supply assumption for telaprevir, since the total recommended duration of therapy is only 84 days, compared with 168 days for the other 2 medications. Finally, the 33 patients dropped because their geographical locations were coded as "unknown" were added back into the analytic sample and the multivariate modeling was performed.

Results

The patient selection procedure is outlined in Figure 1. A total of 13,130 patients had at least 1 hepatitis C prescription claim between January 1, 2012, and July 30, 2012. Of these, 9,013 patients were continuously eligible for pharmacy benefits 180 days before and 365 days after their index hepatitis C claims in 2012. A further 4,736 patients were excluded because they were non-naïve (i.e., they had 1 or more hepatitis C claims during the 180 days prior to their index hepatitis C claims in 2012. The 4,277 remaining patients consisted of 2,557 patients on 3-drug regimens with telaprevir, 1,025 patients on 2-drug regimens, and 695 patients on 3-drug regimens with boceprevir. An additional 1,049 patients were excluded for not exclusively using a specialty or a retail pharmacy. After excluding an additional 33 patients whose geographical locations based on the U.S. Census regions were coded as "unknown," the final analytic sample included 1,475 patients on 3-drug regimens with telaprevir. Of these, 1,182 patients were in the specialty pharmacy group, and the remaining 293 patients were in the retail pharmacy group.

TABLE 1 Characteristics of Study Subjects, PBM Claims Data, 2011 to 2013

Characteristic	Total Study Sample (N = 1,475)		Specialty Pharmacy (n = 1,182)		Retail Pharmacy (n = 293)		*P* Value (Specialty Pharmacy vs. Retail Pharmacy)
	Mean/ Proportion	SD	Mean/ Proportion	SD	Mean/ Proportion	SD	
Age (years)	53.97	8.86	53.85	8.76	54.44	9.27	0.3093[a]
Gender (% female)	37.42		37.82		35.84		0.5305[b]
Out-of-pocket pharmacy spend per 30-day adjusted hepatitis C claim ($)	109.41	349.93	101.48	259.76	141.37	586.46	0.2564[a]
Medication burden (count of unique GPI2s in study period)	8.42	4.52	8.38	4.48	8.58	4.67	0.4913[a]
Days' supply per hepatitis C prescription	31.13	9.89	31.39	10.30	30.09	7.97	0.0188[a,c]
Geographical region of residence (%)							
Northeast	32.27		28.00		49.48		<0.001[b,c]
Midwest	20.00		19.97		20.14		
South	35.66		39.34		20.82		
West	12.07		12.69		9.56		
Percentage of patients persistent at day 168 of therapy	52.81		56.01		39.93		<0.001[b,c]

[a]*Student's t-test.*
[b]*Chi-square test.*
[c]*Significant at P < 0.05.*
GPI2 = 2-digit Medi-Span Generic Product Identifier code; PBM = pharmacy benefit management company; SD = standard deviation.

The demographic and clinical characteristics of the selected patients are found in Table 1. The average patient age was approximately 54 years for both groups. A little over one-third of patients in both groups were female. About 36% of patients using the PBM specialty pharmacy resided in the South compared with just over 20% of retail pharmacy patients. Nearly half of all retail pharmacy patients resided in the Northeast. Days' supply per unadjusted hepatitis C prescription was, on average, 1.3 days higher in the specialty pharmacy group compared with the retail pharmacy group. Out-of-pocket spending per 30-day adjusted hepatitis C prescription and medication burden was not significantly different between the study groups. The percentage of patients persistent to 3-drug hepatitis C regimens containing telaprevir at day 168 (week 24) of therapy was 16.1 percentage points higher among patients using the specialty pharmacy compared with those using retail pharmacies (56.0% vs. 39.9%, $P < 0.001$; Figure 2).

Patients in the specialty group had a higher likelihood of achieving persistence to the 3-drug hepatitis C regimen containing telaprevir at day 168 (week 24) of therapy compared with the retail group (unadjusted odds ratio [OR] = 1.92, 95% confidence interval [CI] = 1.48-2.49). Patient demographics have been found to be significant confounders in assessing the relationship between dispensing channel and medication persistence.[21] Previous research on chronic conditions of diabetes, hypertension, or high blood cholesterol suggest that patients who are either female or living in the Northeast have better adherence. Our study had similar findings. However, previous research found older individuals more likely to be adherent, whereas our results suggest younger adults were more adherent. Results from the multivariate adjusted model are

FIGURE 2 Persistency Measurements by Pharmacy Channel

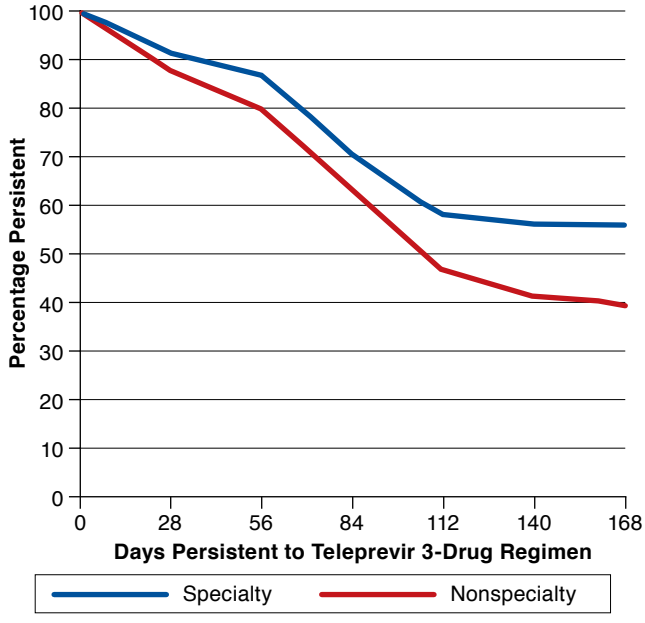


TABLE 2 Logistic Regression Model for Persistence to 3-Drug Hepatitis C Regimens Containing Telaprevir at Treatment Day 168 (Week 24), PBM Claims Data, 2011 to 2013

Variable	Reference Category (for Categorical Variables)	Parameter Estimate	Standard Error	Wald Chi-square	*P* > Chi-square	Odds Ratio Estimate[a]	95% Confidence Limits	
Intercept		-0.249	0.410	0.369	0.544			
Channel (specialty pharmacy)	retail pharmacy	0.636	0.138	21.299	<0.0001	1.889	1.442	2.475
Patient age		-0.017	0.006	7.352	0.007	0.983	0.971	0.995
Gender (female)	Male	0.382	0.112	11.556	0.001	1.466	1.176	1.827
Geographical region of residence								
Midwest	South	0.179	0.150	1.428	0.232	1.196	0.892	1.605
Northeast	South	0.044	0.133	0.108	0.743	1.045	0.804	1.357
West	South	0.008	0.178	0.002	0.963	1.008	0.711	1.429
Medication burden (unique GPI2s in postperiod)		-0.017	0.012	1.984	0.159	0.983	0.960	1.007
Days' supply per unadjusted hepatitis C prescription		0.022	0.006	12.194	0.001	1.022	1.010	1.034
Out-of-pocket pharmacy spend per 30-day adjusted hepatitis C claim		-0.0005	0.0002	4.587	0.032	1.000	0.999	1.000

[a]*Odds of persistence to hepatitis C regimen.*

GPI2 = 2-digit Medi-Span Generic Product Identifier code; PBM = pharmacy benefit management company.

presented in Table 2. After multivariate adjustment, patients in the specialty pharmacy group were 89% more likely to be persistent with the 3-drug regimen containing telaprevir at day 168 (adjusted OR = 1.89, 95% CI = 1.44-2.48). As in the main analysis, patients in the specialty pharmacy group were found to be significantly more likely to be persistent to a 3-drug regimen containing telaprevir compared with patients using retail pharmacy in all scenarios evaluated in the sensitivity analyses.

Discussion

The primary study objective was to determine whether there were differences in 3-drug hepatitis C regimen persistence between patients exclusively using either specialty or retail pharmacies to receive their medications. Our findings showed that after adjusting for a number of known confounders, patients who used a single specialty pharmacy exclusively had 89% greater likelihood of higher 3-drug telaprevir-containing regimen persistence than patients who exclusively used a retail pharmacy. Results were robust to sensitivity analyses in which patients were defined as persistent even when they filled 80% or 90% of the days' supply of hepatitis C medication to be taken by treatment week 24 (day 168). Measuring persistence at treatment day 168 allowed the inclusion of all patients on telaprevir.

Although the AASLD released new guidelines in early 2014, recommending a change from teleprevir to sofosbuvir or simeprevir, the newer regimen guidelines still comprised multidrug treatment (e.g., sofosbuvir, weight-based ribavirin, and weekly pegylated interferon for 12 weeks). Research suggests that treatment complexity is negatively associated with medication persistence. Additionally, research suggests that medication cost may influence patient adherence. Thus, for patients prescribed the newer high-cost hepatitis C agents (sofosbuvir and simeprevir), specialty pharmacy may be an option to assist patients in successfully completing therapy.

There are a number of potential reasons why patients using a specialty pharmacy may be more successful at being persistent to hepatitis C therapy compared with those using a retail pharmacy. Patients using the specialty pharmacy in our study had their hepatitis C medications conveniently delivered to the location of their choice and received timely refill reminders tailored to the telaprevir-based regimen. Patients were also supported by specially trained pharmacists and nurses who provided extensive regimen-specific education, administration training, and coping tips throughout their treatment. In addition, patients received scheduled, telephonic follow-up outreaches to ensure rapid resolution of any concerns or questions.

The specialty pharmacy in this study also coordinated with prescribers to ensure that treatment was continued appropriately and that treatment interruptions were minimized. In addition to ensuring appropriate therapy continuation, the specialty pharmacists actively monitored viral response to treatment and engaged with prescribers to ensure timely discontinuation of regimens meeting futility end points. Although clinically appropriate, efforts to stop therapy when determined to be futile may have reduced the observed persistence rates in the specialty pharmacy group. Nonetheless, this study found higher rates of persistence in the specialty pharmacy group, compared with the retail pharmacy group. Specific retail pharmacies may have offered similar services provided by the specialty pharmacy to hepatitis C patients.

TABLE 3 Comparison of Results from Sensitivity Analyses of Logistic Regression Model for Persistence to 3-Drug Hepatitis C Regimens Containing Telaprevir at Treatment Day 168 (Week 24), PBM Claims Data, 2011 to 2013

Scenario	Specialty Pharmacy		Retail Pharmacy		Adjusted[a] Odds of Persistence in Specialty Pharmacy Compared with Retail Pharmacy	95% Confidence Limits	
	N	% Persistent	N	% Persistent			
Main model	1,182	56.01	293	39.93	1.889	1.442	2.475
Redefined persistence as having filled at least 90% supply of telaprevir (76 days' supply) and pegylated interferon and ribavirin (152 days' supply each) at treatment day 168.	1,182	57.19	293	48.12	1.367	1.046	1.786
Redefined persistence as having filled 100% supply of telaprevir (84 days' supply) and at least 90% supply of pegylated interferon and ribavirin (152 days' supply each) at treatment day 168.	1,182	57.11	293	48.12	1.364	1.044	1.782
Redefined persistence as having filled at least 80% supply of telaprevir (68 days' supply) and pegylated interferon and ribavirin (135 days' supply each) at treatment day 168.	1,182	65.74	293	54.95	1.514	1.155	1.984
Redefined persistence as having filled 100% supply of telaprevir (84 days' supply) and at least 80% supply of pegylated interferon and ribavirin (135 days' supply each) at treatment day 168.	1,182	65.57	293	54.61	1.530	1.168	2.005
Add 33 patients with geographical location coded as "unknown" to study sample	1,215	56.41	323	40.13	1.901	1.455	2.483

[a]*All models adjusted for patient age, patient gender, geographic location, medication burden, days' supply per unadjusted prescription, and out-of-pocket pharmacy spend per 30-day adjusted hepatitis C claim.*

PBM = pharmacy benefit management company.

Limitations

This study has several limitations, many of which are derived from the exclusive use of pharmacy claims data for this analysis. HCV genotype information was not available for study patients; neither were medical claims and laboratory test results. All study patients using the 3-drug regimen were assumed to be appropriate. Since medication burden was used as a proxy for comorbidity burden, conditions in which treatment does not involve medication use might be underrepresented. Examples include nonoral chemotherapy treatments and conditions identified through administrative claims for durable medical equipment, such as urinary incontinence and ostomy product.[22] We used a possession-based measure of regimen persistence, assuming that medication possessed by the patient would be used as prescribed. Similar assumptions have been made in other studies of medication persistence based on prescription claims data.[17] An additional limitation is the presence of several uncontrolled confounders related to pharmacy benefit design: auto-refill programs, channel incentive programs, and copayment tier structure. The specialty pharmacy did not have an auto-refill program in place; however, we could not identify patients engaged in retail auto-refill programs, so our estimates of retail persistence might be inflated, and our study conclusions conservative. Benefit design and channel incentive vary significantly across client populations; thus, the extent to which incentives exist to promote the use of one particular pharmacy channel over another may impact the generalizability of this study. Additionally, some patients may have been required to continue therapy until treatment day 336 (48 weeks), which is not considered here. We were unable to control for the effect of the distribution of patient race, which has been shown to be an important determinant of treatment response and tolerability.[11,23,24] Further research may be needed to examine the impact of age and adherence to medications treating longer-term acute conditions, such as hepatitis C. Finally, although the analysis did not examine the most recent HCV guidelines, the analysis did examine the relationship between a complicated 3-drug regimen in the treatment of hepatitis C. We believe our findings to be applicable to the current HCV treatment guidelines, which requires the use of multiple medications for the treatment of HCV genotype I.

Conclusions

This study found that patients using a specialty pharmacy that offered a disease-specific hepatitis C care management program were 89% more likely to be persistent to 3-drug hepatitis C regimens containing telaprevir until an important clinical milestone, at treatment day 168 (week 24). Plan sponsors, payers, and patients may benefit from the hepatitis C specific care model used by the specialty pharmacy evaluated in this study for newer hepatitis C therapies, such as simeprevir and sofosbuvir.

Authors

ROCHELLE R. HENDERSON, PhD, MPA, is Senior Director, Research and Analytics; REBECCA J. LEVIN, MS, is Director, Research and Analytics; and SHARON GLAVE FRAZEE, PhD, MPH, is Vice President, Research and Analytics, Express Scripts Holding Company, St. Louis, Missouri. GAIL G. BRIDGES, PharmD, is Senior Manager, Clinical Program Management, and MARY DORHOLT, PharmD, is Senior Director and Clinical Practice Lead, Accredo Specialty Pharmacy, Memphis, Tennessee. JAY VISARIA, PhD, MPH, is Research Manager, HealthCore, Wilmington, Delaware.

AUTHOR CORRESPONDENCE: Sharon Glave Frazee, PhD, MPH, One Express Way, 2W05, St. Louis, MO 63134. E-mail: SEFrazee@express-scripts.com.

DISCLOSURES

Funding for this study was provided internally by Express Scripts. Henderson, Levin, and Glave Frazee are employees of Express Scripts Holding Company; Visaria was employed by Express Scripts at the time this research was conducted. Bridges and Dorhold are employees of Accredo Specialty Pharmacy.

Concept and design were contributed by Visaria, Henderson, Glave Frazee, Dorholt, and Bridges. Visaria and Levin collected the data; statistical analysis was done by Visaria, Henderson, and Glave Frazee; and Visaria, Henderson, Levin, Bridges, and Glave Frazee interpreted the data. The manuscript was written by Visaria, Henderson, Levin, Bridges, and Glave Frazee and revised by Visaria, Henderson, Levin, Bridges, Dorholt, and Glave Frazee.

ACKNOWLEDGMENTS

The authors thank Doug Mager, MS; Scott Micek, PharmD; and Yuhong Tian, PhD, for providing assistance with the analysis.

REFERENCES

1. Ditah I, Ditah F, Devaki P, et al. The changing epidemiology of hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2001 through 2010. *J Hepatol.* 2014;60(4):691-98.

2. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med.* 2014;160(5):293-300.

3. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-21.

4. U.S. Food and Drug Administration. Approval of Incivek (telaprevir), a direct acting antiviral drug (DAA) to treat hepatitis C (HCV). May 23, 2011. Available at: http://www.natap.org/2011/HCV/telap_02.htm. Accessed November 5, 2014.

5. U.S. Food and Drug Administration. FDA approves Victrelis for hepatitis C. Press release. May 13, 2011. Available at: http://www.fda.gov/newsEvents/Newsroom/PressAnnouncements/ucm255390.htm. Accessed October 24, 2014.

6. Jensen DM. A new era of hepatitis C therapy begins. *N Engl J Med.* 2011;364(13):1272-74.

7. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype I chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011;54(4):1433-44.

8. Theodorou AA, Szychowski JA, Sehman ML, Swarna V. Initial prescription utilization of the new hepatitis C agents. *Am J Pharm Benefits.* 2012;4(2):80-83.

9. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol.* 2012;107(5):669-89.

10. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C—June 10-12, 2002. *Hepatology.* 2002;36(5 Suppl 1):S3-S20.

11. Manos MM, Darbinian J, Rubin J, et al. Effect of hepatitis C treatment response on medical costs: a longitudinal analysis in an integrated care setting. *J Manag Care Pharm.* 2013;19(6):438-47. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=16750.

12. American Association for the Study of Liver Diseases. Recommendations for testing, managing, and treating hepatitis C. Revised October 8, 2014. Available at: http://www.hcvguidelines.org/fullreport. Accessed October 24, 2014.

13. Lieveld FI, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. *Ann Hepatol.* 2013;12(3):380-91.

14. Tungol A, Rademacher K, Schafer JA. Formulary management of the protease inhibitors boceprivir and telaprevir for chronic hepatitis C virus. *J Manag Care Pharm.* 2011;17(9):685-94. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=13668.

15. Visaria J, Frazee SG. Role of pharmacy channel in adherence to hepatitis C regimens. *Am J Pharm Benefits.* 2013;5(1):17-24.

16. Cohen SM, Kwasny MJ, Ahn J. Use of specialty care versus standard retail pharmacies for treatment of hepatitis C. *Ann Pharmacother.* 2009;43(2):202-09.

17. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008;11(1):44-47.

18. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guidelines by the American Association for the Study of Liver Disease. *Hepatology.* 2011;54(4):1433-44.

19. U.S. Census Bureau. Geographic terms and concepts: census divisions and census regions. Last revised April 25, 2013. Available at: https://www.census.gov/geo/reference/gtc/gtc_census_divreg.html. Accessed November 5, 2014.

20. Visaria J, Henderson RR, Frazee SG. Specialty pharmacy improves adherence to imatinib. *Am J Pharm Benefits.* 2013;5(Special Issue):SP33-SP39.

21. Iyengar R, Henderson R, Visaria J, Glave Frazee S. Dispensing channel and medication adherence: evidence across 3 therapy classes. *Am J Manag Care.* 2013;19(10):798-804.

22. Farley JF, Harley CR, Devine JW. A comparison of comorbidity measurements to predict healthcare expenditures. *Am J Manag Care.* 2006;12(2):110-19.

23. Kinzie JL, Naylor PH, Nathani MG, et al. African Americans with genotype 1 treated with interferon for chronic hepatitis C have a lower end of treatment response than Caucasians. *J Viral Hepat.* 2001;8(4):264-69.

24. Missiha S, Heathcote J, Arenovich T, Khan K; Canadian Pegasys Expanded Access Group. Impact of Asian race on response to combination therapy with peginterferon alfa-2a and ribavirin in chronic hepatitis C. *Am J Gastroenterol.* 2007;102(10):2181-88.

APPENDIX List of Hepatitis C Medications Used in Analysis

Drug Name	National Drug Code Number	Drug Name	National Drug Code Number	Drug Name	National Drug Code Number
Telaprevir	51167010001	Ribavirin	00004008694	Ribavirin	54868452102
Interferon Alfacon-1	66435020209	Ribavirin	54868488800	Ribavirin	54738095342
Interferon Alfacon-1	64116003106	Ribavirin	00085132704	Ribavirin	54738095370
Interferon Alfacon-1	55513055406	Ribavirin	54868503500	Ribavirin	68382004603
Interferon Alfacon-1	00187200706	Ribavirin	00085138507	Ribavirin	00781204342
Interferon Alfacon-1	66435020115	Ribavirin	00085119403	Ribavirin	00406226056
Interferon Alfacon-1	64116003124	Ribavirin	00085131801	Ribavirin	65862029042
Interferon Alfacon-1	00187200702	Ribavirin	00085135105	Ribavirin	68382004610
Interferon Alfacon-1	66435020199	Ribavirin	66435010856	Ribavirin	00406226070
Interferon Alfacon-1	55513056201	Ribavirin	66435010599	Ribavirin	59930152302
Interferon Alfacon-1	55513056206	Ribavirin	49884033876	Ribavirin	54738095356
Interferon Alfacon-1	55513055401	Ribavirin	49884034076	Ribavirin	54738095016
Interferon Alfacon-1	55513092606	Ribavirin	49884007176	Ribavirin	68382004628
Interferon Alfacon-1	64116003906	Ribavirin	66435010799	Ribavirin	68084017911
Interferon Alfacon-1	66435020196	Ribavirin	66435010656	Ribavirin	54738095256
Interferon Alfacon-1	55513092706	Ribavirin	66435010556	Ribavirin	00781204316
Interferon Alfacon-1	64116003901	Ribavirin	66435010699	Ribavirin	68084015011
Interferon Alfacon-1	00187200601	Ribavirin	66435010899	Ribavirin	65862029018
Interferon Alfacon-1	55513092601	Ribavirin	66435010756	Ribavirin	54868452101
Interferon Alfacon-1	64116003101	Ribavirin	49884085656	Ribavirin	00093722777
Interferon Alfacon-1	55513092701	Ribavirin	49884085693	Ribavirin	68382026004
Interferon Alfacon-1	66435020295	Ribavirin	49884085694	Ribavirin	00093722758
Interferon Alfacon-1	66435020195	Ribavirin	66435010356	Ribavirin	65862029084
Interferon Alfacon-1	00187200605	Ribavirin	66435010170	Ribavirin	00093722763
Interferon Alfacon-1	64116003924	Ribavirin	66435010142	Ribavirin	68382026009
PegInterferon Alfa-2a	00004035039	Ribavirin	54868452100	Ribavirin	68382026012
PegInterferon Alfa-2a	54868488701	Ribavirin	66435010184	Ribavirin	68382012807
PegInterferon Alfa-2a	00004035239	Ribavirin	49884085692	Ribavirin	00406226042
PegInterferon Alfa-2a	00004035730	Ribavirin	66435010216	Ribavirin	68084015065
PegInterferon Alfa-2a	00004035009	Ribavirin	66435010456	Ribavirin	59930152304
PegInterferon Alfa-2a	54868488700	Ribavirin	66435010118	Ribavirin	00781517728
PegInterferon Alfa-2a	00004036530	Ribavirin	66435010156	Ribavirin	68382026028
PegInterferon Alfa-2a	00004036030	Ribavirin	16241033776	Ribavirin	00093722772
PegInterferon Alfa-2b	00085136801	Ribavirin	16241006976	Ribavirin	54868452103
PegInterferon Alfa-2b	00085129101	Ribavirin	16241007056	Ribavirin	68084017965
PegInterferon Alfa-2b	00085127901	Ribavirin	16241006956	Ribavirin	68382012907
PegInterferon Alfa-2b	00085130401	Ribavirin	16241007076	Ribavirin	65862029070
PegInterferon Alfa-2b	00085132301	Ribavirin	00093723281	Ribavirin	65862020768
PegInterferon Alfa-2b	54868503601	Ribavirin	68382012707	Ribavirin	00781204304
PegInterferon Alfa-2b	00085137002	Ribavirin	68382026007	Ribavirin	59930152301
PegInterferon Alfa-2b	00085132302	Ribavirin	54738095384	Ribavirin	59930152303
PegInterferon Alfa-2b	54868503600	Ribavirin	54738095156	Ribavirin	00781204367
PegInterferon Alfa-2b	00085131601	Ribavirin	49884004532	Ribavirin	54738095318
PegInterferon Alfa-2b	00085129701	Ribavirin	68382026010	Ribavirin	53095000701
PegInterferon Alfa-2b	00085131602	Ribavirin	65862029056	Ribavirin	00187000701
PegInterferon Alfa-2b	00085129702	Ribavirin	00406204616	Ribavirin	00187000714
PegInterferon Alfa-2b	00085137001	Ribavirin	00406226084	Ribavirin	53095000714