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RESEARCH NOTES

Local specialty pharmacy and specialty clinic collaboration assists access to hepatitis C direct-acting antivirals

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ABSTRACT

Objectives: To measure prescribed time to therapy (TtT) and sustained virologic response (SVR). Secondary objectives were to assess insurance appeals and copay assistance amount facilitated by a local specialty pharmacy (LSP).

Methods: This descriptive, retrospective study used a joint clinical and pharmacy database of patients who were prescribed direct-acting antivirals (DAAs) at a single-center liver specialty clinic and received LSP services from December 2013 to December 2015.

Results: Among 388 patients prescribed DAAs, 364 (94%) patients, who were 18 years of age or older, initiated DAA therapy, and received LSP services, were included in the study. Of these, 211 (58.0%) had cirrhosis, 159 (43.7%) had previous treatment, and 57 (15.7%) had previous liver transplants. Most patients had commercial insurance (n = 249; 68.4%), and 295 (81.0%) required prior authorization. Insurance initially denied coverage to 70 patients (19.2%), for who the LSP drafted appeals for 60 (85.7%). Copay information was available for 154 LSP patients. Although 66 had initial copays of more than $20 per month, the LSP was able to assist most (98.1%; n = 151) with copay reductions to $20 or less. Full financial assistance was received for 20 patients without insurance or any DAA coverage. Among 171 patients with SVR and prescribed TtT information, mean TtT was 12 days (median 4 days), and most received medications within 10 days (n = 122; 71.3%). The overall intention-to-treat SVR rate was 86.8%; the per-protocol (PP) SVR rate was 93.8%.

Conclusion: Collaboration between providers and an LSP minimized delay in therapy, lowered rates of DAA denial, facilitated patient financial assistance, and helped to optimize clinical outcomes. The PP-SVR rate for this study was similar to rates reported in the literature and higher than expected, considering the inclusion of earlier-generation DAAs and many patients with advanced liver disease.

The hepatitis C virus (HCV) is the most common bloodborne pathogen and the leading cause of liver transplantation and liver cancer in the United States. According to the Centers for Disease Control and Prevention, about 30,500 acute infections occur each year, and an estimated 2.7 to 3.9 million people live with chronic HCV.[1] Six major genotypes and more than 70 different HCV subtypes have been identified. Of these, genotype 1 (subtypes 1a, 1b) is most common in the United States, followed by genotypes 2 and 3.[2]

Before direct-acting antiviral (DAA) therapies were introduced, HCV was treated with the use of pegylated interferon + ribavirin (PegIFN+RBV)–based regimens, which had more severe adverse effects, a negative impact on quality of life, and higher treatment failure rates.[3] DAA oral combination regimens approved in 2013 and 2014 dramatically improved cure rates with minimal adverse effects and shorter treatment

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duration than earlier therapies.[3,4] DAAs are now the first-line therapy recommended by the American Association of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA).[5] In the AASLD/IDSA treatment guidelines, a primary goal of treatment of people infected with HCV is to achieve virologic cure as evidenced by a sustained virologic response (SVR).[5-7] The cure rates of DAA regimens exceed 90% for all HCV genotypes,[3] whereas the efficacy of PegIFN+RBV–based regimens was approximately 40% to 50% for genotype 1.[3,8]

Access to DAA therapy is a key component in achieving SVR and is negatively affected by many factors, including high costs, lack of adequate insurance coverage, patient ineligibility for treatment based on insurance restrictions, and high burden of paperwork.[9] The average wholesale acquisition cost of a 12-week course of Food and Drug Administration–approved therapy ranged from $54,600 to $147,000.[10-13] A recent study demonstrated the real-world mean drug cost per SVR was $147,348 for all patients but varied by fibrosis stage.[14] Given high demand and costs of DAAs, some insurers and state Medicaid programs implement prior authorization requirements that restrict immediate access for certain patients.[9,10] A retrospective chart review showed that nearly 25% of patients who were prescribed sofosbuvir (SOF)–ledipasvir (LDV) were initially denied access to DAA therapies, thus delaying initiation of treatment.[9]

Objectives

Limited evidence in the literature exists about local specialty pharmacies' (LSPs) role in reducing barriers to DAA access and achieving clinical outcomes. The primary objectives of this study were to measure prescribed time to therapy (TtT) and SVR; the secondary objectives were to assess insurance appeals and copay assistance amount facilitated by an LSP.

Methods

Study design and patients

This study was a descriptive, retrospective study of patients prescribed DAAs for treating HCV at a single-center liver specialty clinic in Atlanta, GA. All patients were automatically enrolled in the pharmacy intervention program with an opt-out option. Patients were included in the study if they received LSP services from December 2013 to December 2015, were 18 years of age or older, and had at least 1 pharmacy prescription for DAA therapies. Regimens included were SOF (Sovaldi; Gilead Sciences), SOF/LDV (Harvoni; Gilead Sciences), simeprevir (SMV; Olysio; Janssen Pharmaceuticals), daclatasvir (DCV; Daklinza; Bristol-Myers Squibb), and paritaprevir-ritonavir-ombitasvir-dasabuvir (PrOD) tablets (Viekira Pak; AbbVie). Additional HCV medications included in the analysis were SOF in combination with PegIFN+RBV. Patients who did not initiate therapy were excluded. This research was approved by the Quorum Institutional Review Board (#30978/1) and Piedmont Healthcare Institutional Review Board (#829445/6).

Pharmacy intervention

The LSP in this study was part of a larger pharmacy chain with a network of HCV-specialized LSPs. Pharmacists at network LSPs were specially trained in the clinical aspects of HCV care and the importance of improving access and affordability to DAAs. Patients in these LSPs were proactively managed via a pharmacy-based therapy management program or chart review that focused on patient adherence and therapy completion. These services included the following:

- Before therapy initiation, a medication history was obtained for all patients, and appropriate interventions were taken to prevent potential drug interactions. Pharmacists coordinated with the clinic to facilitate the prior authorization process and proactively helped to manage renewals and appeals.
- Like other HCV-specialized LSPs, this Atlanta-based pharmacy managed the prior authorization, appeals, and financial assistance for new HCV prescriptions in collaboration with the clinic. Financial assistance included manufacturer copay cards, nonprofit organizations, foundational assistance, and various manufacturer patient assistance programs.
- Once DAA therapy was initiated, pharmacists called patients within 1 to 2 days of initial medication fill to record actual start date. Seven days before a refill, pharmacists contacted patients as a refill reminder and to identify any further financial assistance needs. Every 4 weeks, pharmacists checked for patient adverse effects or adverse events, which were also communicated to the specialty clinic.
- Pharmacists called patients to ensure that patients completed a full course of treatment 7 days before viral load tests and contacted physicians for viral load results.

All of the above interventions were completed regardless of LSP third-party contractual ability to provide medication to referred patients.

Outcome measures

The primary outcomes were prescribed TtT and SVR; secondary outcomes were LSP-facilitated copay assistance and the number of appeals of initial insurance denial. Prescribed TtT was computed as the difference between the first prescription date and index fill of DAA medications; outliers above 3 times the standard deviation were excluded. SVR rate was measured as the percentage of patients with an unquantifiable HCV RNA 12 weeks or more after completing DAA therapy. SVR rates were calculated with the use of both intention-to-treat (ITT) and per-protocol (PP) methods. The ITT rates included all patients who started therapy and received at least 1 dose of DAA therapy; the PP rate excluded those lost to follow-up or deceased. The copay assistance outcome was measured as the average patient out-of-pocket costs before and after LSP-facilitated assistance. The number of denials and appeals were measured as required prior authorization for DAA; DAA therapy initially denied by insurance; LSP-facilitated appeals for initial insurance denials; and final denials but not appealed.

Data collection and descriptive analysis

Retrospective chart reviews were conducted for all patients with HCV to collect baseline demographic characteristics, clinical data, and insurance status. Mean (and/or median) with standard deviation or confidence interval was provided for

Table 1
Baseline characteristics of patients

Characteristic	Patients who initiated therapy (n = 364)		LSP patients with both TtT and SVR data (n = 171)	
	n[a]	%	n	%
Male	226	62.1%	108	63.2%
Age, y (mean ± SD)	364	58.1 ± 8.0	171	58.0 ± 7.7
Race				
White	228	62.6%	97	56.7%
Black/African American	120	33.0%	64	37.4%
Other	16	4.4%	10	5.8%
Liver cirrhosis	211	58.0%	98	57.3%
Previous treatment failure	159	43.7%	72	42.1%
Liver transplant recipient	57	15.7%	31	18.1%
Insurance type				
Commercial	249	68.4%	98	57.3%
Medicare	64	17.6%	45	26.3%
Medicaid	32	8.8%	28	16.4%
Other	13	3.6%	0	0.0%
No insurance	6	1.6%	0	0.0%
HCV genotype				
1 (a/mixed/unknown)	245	67.3%	118	69.0%
1b	71	19.5%	33	19.3%
2, 3, or 4	48	13.2%	20	11.7%
Prescribed treatment regimen				
LDV-SOF (±RBV)	218	59.8%	107	62.6%
PrOD	23	6.3%	9	5.3%
SOF+RBV	41	11.3%	14	8.2%
SOF+SMV (±RBV)	57	15.7%	26	15.2%
SOF+DCV	8	2.2%	5	2.9%
SOF-IFN-RBV	17	4.7%	10	5.8%

Abbreviations used: LSP, local specialty pharmacy; TtT, time to therapy; SVR, sustained virologic response; HCV, hepatitis C; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; PrOD, paritaprevir-ritonavir-ombitasvir-dasabuvir; SMV, simeprevir; DCV, daclatasvir; IFN, interferon.

[a] Counts do not equal the total, owing to missing data.

continuous variables. Count and percentage of patients were provided for all categorical variables. The Mantel-Haenszel chi-square test was used to examine the association between the prescribed TtT and SVR; TtT was categorized into 3 groups: 0 to 10 days, 11 to 29 days, and 30 days or more. All data were analyzed with the use of SAS Enterprise Guide 7.1.

Results

Patient baseline characteristics and outcomes are presented in Tables 1 and 2. Of the 388 patients prescribed DAAs, 24 (6.2%) never initiated therapy; 364 patients (93.8%) who initiated therapy were followed until the end of treatment. The denominators of ITT-SVR and PP-SVR were similar. Of the 364 patients followed until the end of therapy, 337 (92.6%) completed a full course of therapy. Data on prescription fills and LSP-facilitated financial assistance were available for 364 patients (93.8%) who filled at least 1 DAA prescription. Although 225 (61.8%) patients were able to fill DAAs at the LSP, 139 patients (38.2%) were required to fill DAAs at a different pharmacy owing to insurance requirements (Supplemental Figure 1).

The ITT-SVR rate was 86.8% (316/364), and the PP-SVR rate was 93.8% (316/337). The ITT rate included 15 patients in the denominator who were lost to follow-up and 12 patients who died, whereas the PP rate excluded those patients from the denominator (Supplemental Figure 1). The PP-SVR rate was numerically higher for several patient subpopulations, including those who were treatment naive (96.3%) and without cirrhosis (97.3%; Supplemental Table 1).

Of the 171 LSP patients with both prescribed TtT and SVR rate information available, the average prescribed TtT was 12 ± 18 days (median 4 days), with a maximum of 86 days. TtT varied by several patient characteristics. Average TtT for initially approved patients was 7 days, compared with 50 days for patients requiring DAA appeals. TtT for Medicaid was 26 days, which was longer than both commercial insurance (14 days) and Medicare (11 days). SOF and RBV therapies had the shortest TtT (4 days), whereas PrOD had the highest TtT (36 days; Supplemental Table 1). PP-SVRs by TtT were 96.7% for 0 to 10 days, 96.4% for 11 to 29 days, and 81.0% for 30 days or more; higher SVR rates were associated with a lower prescribed TtT ($P = 0.0283$; Table 2).

Among 70 patients who were initially denied prior authorizations, the LSP appealed 60 initial denials, and their final PP-SVR rate was 88.5% (53/60). For 10 patients whose initially denied regimens were not appealed, the majority were switched to different regimens, and their final PP-SVR rate was 61.5% (5/9) (Supplemental Figure 1). Among 154 patients with copay information available, 66 (42.8%) had monthly copays of more than $20 (Table 2). After LSP copay assistance was conducted, initial monthly copays of more than $20 declined to $5 or less for 63 (95.5%) of 66 patients. In addition, full financial assistance was received through LSP appeal for 20 patients without insurance or any DAA coverage.

Discussion

This study demonstrated that a high PP-SVR rate of 93.8% is achievable in a hepatology clinic patient population with the use of LSP assistance. Although this SVR rate was similar to SVR rates published in DAA trials,[15] our "real-world" patient population included a heterogeneous mix of HCV genotypes, prescribed treatment regimens, and patient characteristics, with a higher proportion of patients with advanced liver disease, previous treatment failure, and previous liver transplants. In other

Table 2
Patient outcomes

Outcome measure	n	%
SVR rate		
ITT-SVR	316/364	86.8%
PP-SVR	316/337	93.8%
SVR rate by TtT[a,b]		
0–10 d	118/122	96.7%
11–29 d	27/28	96.4%
≥ 30 d	17/21	81.0%
Monthly copay		
Initial copay ≤ $20 per mo	88/154	57.1%
Final copay after financial assistance ≤ $20 per mo	151/154	98.1%
DAA approval outcomes		
Required prior authorization for DAA	295/364	81.0%
DAA therapy initially denied by insurance	70/364	19.2%
LSP-facilitated appeals for initial insurance denials	60/364	16.5%
Final denials, not appealed	10/364	2.7%

Abbreviations used: ITT, intention-to-treat; PP, per-protocol; DAA, direct-acting antiviral; others as in Table 1.

[a] $P = 0.0283$ was significant among SVR rates of 3 prescribed TtT groups.

[b] For 171 LSP patients with both TtT and SVR information available, TtT was 0 to 10 days for 122 patients (71.3%); 11 to 29 days for 28 patients (16.4%); and 30 days or more for 21 patients (12.3%).

"real-world" studies, SVR rates ranged from 90% to 92% for LDV/SOF ± RBV,[16,17] 88% to 92% for ombitasvir-based regimen ± RBV, and 94% for LDV/SOF ± RBV for a study population with higher cirrhosis prevalence.[18] In 2 DAA studies of patients with chronic HCV and decompensated cirrhosis, SVR ranged from 78.1% to 81.6%.[19,20] SVR rates in treatment-naive genotype 1 patients were 56.6% to 65.3% when treated with either boceprevir or telaprevir plus PegIFN+RBV.[21]

The ITT-SVR rate (86.8%) highlights the need to address patient access and adherence at each step of the HCV treatment cascade. Twenty-seven patients in our study were lost to follow-up or died during treatment. The high mortality rate was likely because HCV patients seeking treatment at this hepatology clinic had more advanced liver disease compared with populations in other studies.[22]

We observed a shorter average prescribed TtT (12 ± 18 days) compared with others in the literature. Do et al. found the average time-to-decision of prior authorization requests to be 26 ± 25 days for the general population and 18 ± 21 days for a transplant-clinic population.[9] In another chart review, average TtT was 31 days (median 23 days, interquartile range 14 to 35 days).[23] Rice et al. identified some factors associated with shorter TtT, including infectious diseases clinic management (28 vs. 45 days), absence of other liver disease (28 vs. 61 days), having a public insurance payer (28 vs. 50 days), and initial approval of requested regimen (26 vs. 102 days).[23] In comparison, our study found longer TtT for DAA authorization of initial denials, patients with Medicaid, and specific regimens. Given our small sample with delayed access to therapy and our observational study design, we could not confirm which factors were linked to lower SVR, but future research should consider such hypotheses.

To our knowledge, this is one of the first studies to characterize DAA financial assistance facilitated by an LSP. A recent abstract found that HCV treatment copays ranged from $0 to $27,000 (with an average copay of $320), with only 25% of patients able to obtain copay assistance and the remaining 75% having an average copay of $428.[24] In the present study, although 66 of 154 patients had initial copay amounts of more than $20 per month, the LSP was able to assist a majority of patients with copay reductions to $20 or less and all 20 patients who had no insurance or inadequate insurance coverage.[13] We speculate that this may be the result of collaboration between the hepatology clinic and the LSP by sharing relevant clinical information and working together to overcome insurance hurdles.

This study was performed to describe the collaboration between a clinic that was well versed in evaluating the severity of liver disease and prescribing appropriate treatment regimens and an LSP that facilitated overcoming the complex barriers to obtaining DAA therapy. Our results suggest that such facilitation may be associated with improved access to treatment and optimal SVR rates. The PP-SVR rates of this study were similar to those in the literature and perhaps numerically higher than expected, considering the inclusion of treatment with earlier-generation DAAs and the high proportion of patients with an advanced liver disease, including liver transplant recipients. Moreover, the SVR rate in liver transplant recipients in this "real-world" study was at least as high as those reported in registration trials.[15] Prescribed TtT was 7 times longer for patients requiring prior authorization than those with initial approval. The LSP staff received extensive clinical and prior authorization training in transplantation and virology, which may have further contributed to shorter average prescribed TtT. The LSP assisted patients with appealing DAA denials, helped to shorten prescribed TtT, facilitated patient financial assistance, and reduced patient out-of-pocket costs.

It is critical for specialty pharmacies to be able to collaborate with DAA prescribers and have systems in place to promote access and affordability to DAA therapy for patients. The University of Rochester HCV integrated management program also has revealed high patient adherence rates and high SVR rates for patients participating in a similar integrated hepatitis clinic model.[25] Taken together, these data demonstrated that an HCV-specialized LSP in collaboration with DAA prescribers may play a key role in the successful completion of DAA therapy.

Limitations

The present study had several important limitations. First, the study population was subject to referral bias due to treatment at a single liver specialty clinic in 1 state and may not be representative of all patients seeking treatment for HCV. As an example, few patients coinfected with HIV were included. This limits the generalizability of study findings. Second, the study was observational and the results only descriptive. Because all patients were offered LSP assistance, we could not compare patients who received LSP services with those who did not, which limited comparison with SVR rates from other "real-world" trials. Third, because many patients filled prescriptions outside of the pharmacy network, some variables had a high proportion of missing data, which may have introduced bias if data were not missing at random. Finally, the treatment start dates likely varied by patient.

Conclusion

The effective management of costly DAA therapies seemed to be closely linked to the collaboration among the LSP, specialty clinics, and patients to address insurance barriers. The LSP played an integral role in working with providers and patients to navigate the complex insurance approval process. This LSP was based in the community it served, had expertise in HCV, and was able to administer this pharmacy-based therapy management program. Through collaboration with prescribers, LSPs may be able to improve access and affordability to DAA therapy.

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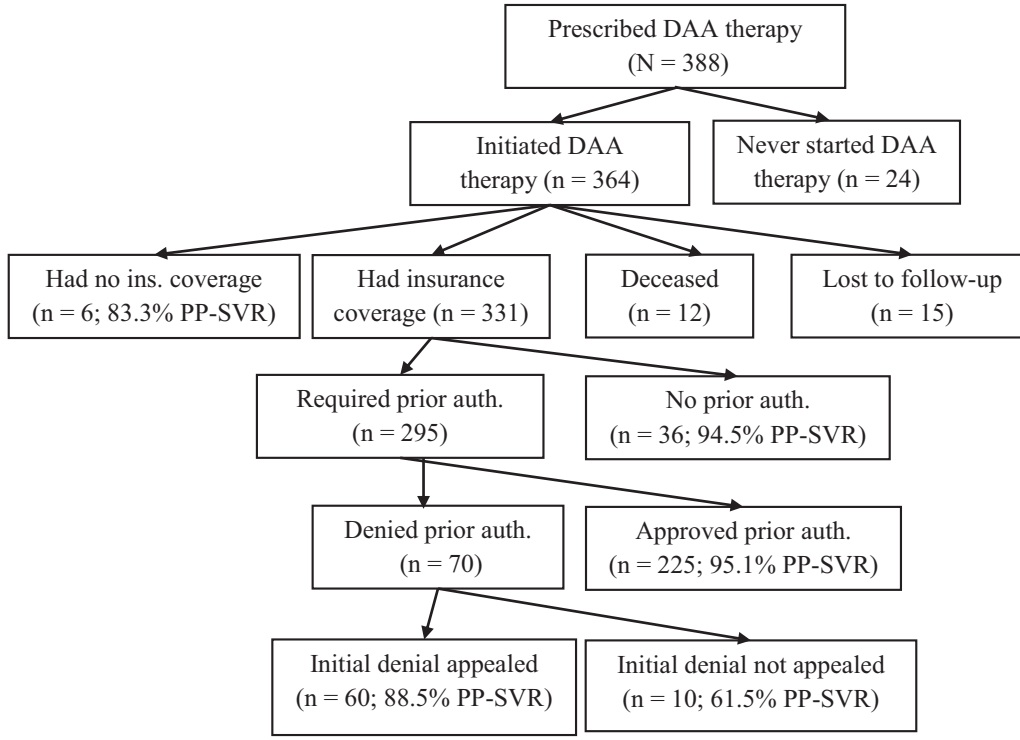
Supplementary data



Supplemental Figure 1. Patient flow chart. Abbreviations used: DAA, direct-acting antiviral agents; SVR, sustained virologic response; PP, per-protocol.

Supplemental Table 1
SVR rate and time to therapy of per-protocol study population by characteristics

Patient characteristic	Per-protocol SVR		Time to therapy[a]	
	n	SVR, % (95% CI)	n	Mean, days (95% CI)
Cirrhosis				
Absent	145/149	97.3 (94.7–99.9)	80	15 (10–21)
Present	171/188	91.0 (86.8–95.1)	105	12 (9–16)
Previous HCV therapy[b]				
Treatment naive	156/162	96.3 (93.4–99.2)	96	15 (10–19)
Previously treated	139/154	90.3 (85.5–95.0)	80	11 (8–14)
Previous live transplantation therapy				
No previous liver transplant	262/281	93.2 (90.3–96.2)	153	16 (11–22)
Liver transplant recipient	54/56	96.4 (91.4–100.0)	33	9 (5–13)
Insurance type				
Commercial	219/236	92.8 (82.7–100)	110	14 (10–18)
Medicare	52/53	98.1 (94.3–100)	47	11 (4–19)
Medicaid	28/30	93.3 (83.9–100)	29	26 (4–47)
Other	17/18	94.4 (89.5–96.1)	NA	NA
Genotype				
HCV 1 (a/mixed/unknown)	211/226	93.4 (90.1–96.6)	128	15 (10–20)
HCV 1b	66/67	98.5 (95.5–100)	37	18 (7–30)
HCV 2, 3, or 4	39/44	88.6 (78.9–98.4)	21	10 (1–18)
Prescribed treatment regimen				
LDV-SOF (±RBV)	189/202	93.6 (90.2–97.0)	116	16 (10–23)
PrOD	20/21	95.2 (85.3–100)	12	36 (4–67)
SOF+RBV	34/38	89.5 (79.3–99.7)	15	4 (1–8)
SOF+SMV (±RBV)	52/54	96.3 (91.1–100)	28	10 (6–14)
SOF+DCV	6/7	85.7 (50.8–100)	5	14 (0–29)
SOF-IFN-RBV	15/15	100 (NA)	10	7 (3–12)
DAA approval				
No prior authorization required	40/42	95.2 (88.5–100)	8	6 (1–12)
DAA prior authorization initially approved	213/224	95.1 (92.2–97.9)	139	7 (5–8)
DAA appeal approved	7/7	100 (NA)	4	26 (0–67)
DAA appeal initially denied	56/64	87.5 (79.2–95.8)	35	50 (31–68)
Length of therapy				
≤12 wk	216/229	94.3 (91.3–97.3)	123	16 (12–20)
>12 wk	100/108	92.6 (87.6–97.6)	63	13 (3–23)

Abbreviations used: SVR, sustained virologic response; CI, confidence interval; HCV, hepatitis C; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; PrOD, paritaprevir-ritonavir-ombitasvir-dasabuvir; SMV, simeprevir; DCV, daclatasvir; IFN, interferon; DAA, direct-acting antiviral.

[a] The time to therapy N may be different from the SVR N due to missing data.

[b] The prior treatment experience data were missing for 21 patients.