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Application of PCSK9 Inhibitors in Practice: Part 2 – The Patient Experience

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Abstract

Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9i) are set to revolutionize the treatment of hypercholesterolemia in the management of atherosclerotic risk, but numerous reports have detailed unprecedented barriers to access for these drugs. To overcome these challenges, our group created a model to facilitate provision of this new therapy for patients who qualify according to FDA criteria. This report details the real-world follow-up experience of PCSK9i use in a large patient cohort structured to ensure rigor in data collection, analysis, and interpretation. The 271 patients approved and actively followed in our PCSK9i clinic between July 2015 and August 2018 represent a 97% approval rate from insurance, with 28% of prescriptions requiring at least one appeal. Over 50% of patients were statin intolerant. On average, there was a median lapse of 15 days between initial visit and insurance approval. PCSK9i therapy was affordable for most patients, with an average monthly out-of-pocket expense of $58.05 (median $0). Only 2.3% of patients were unable to initiate or continue therapy due to cost. Reductions from baseline in LDL cholesterol and Lp(a) were comparable to published reports with median reductions of 60% and 23% at one year, respectively. PCSK9i therapy was well tolerated overall, though 9% of patients reported adverse events, and 5% of patients discontinued due mostly to musculoskeletal and flu-like symptoms. Our practice model demonstrates that PCSK9i therapy can be accessed easily and affordably for the majority of eligible patients, resulting in dramatic improvement in lipid profile results. Moreover, our registry data suggest that results from the prospective clinical

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trials of PCSK9i on LDL and Lp(a) reduction and on tolerability are applicable to a real-world cohort.

Keywords

PCSK9; PCSK9 inhibitors; LDL-cholesterol; Lipoprotein(a); Drug Adherence

Subject codes:

PCSK9 Inhibitors; LDL; Lp(a); Adverse drug effects; Registry

Introduction

Results from landmark clinical outcome trials of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have confirmed the initial excitement for this class of low-density lipoprotein-cholesterol (LDL-C) lowering agents,[1–3] and the "statin hypothesis" has been supplanted by the "LDL hypothesis." Hence, guideline recommendations and consensus statements now endorse the use of PCSK9i as appropriate second or third line agents, or as alternative therapy in cases of complete statin intolerance, for patients with established atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (FH) with persistent hypercholesterolemia.[1–3] As evidence supporting their ability to improve cardiovascular outcomes continues to mount, PCSK9i use will undoubtedly continue to expand given the size of the target population.

Prior reports of PCSK9i treatment have provided details from either the clinical trial perspective,[4–6] the provider perspective,[7–12] or the payer and societal perspectives.[13–18] However, few reports have reflected the patient experience with PCSK9i in clinical use. This is part two of a report that initially described the design and implementation of a dedicated PCSK9i clinic as a means to increase efficiency of referral and access to PCSK9i treatment for patients who meet standard of care indications for this therapy.[7] The goal of this second report is to outline, from the patient's perspective, a real world experience with PCSK9i therapy in relation to accessibility of the drug, out-of-pocket expense, side effects, and lipid-lowering efficacy using a rigorously structured cohort.

Methods

This study derives from pre-planned analyses of a prospectively designed clinical cohort in which subjects were enrolled in the previously reported PCSK9i clinic of our Center for Preventive Cardiology (CPC) at OHSU.[7] Briefly, patients were referred from within OHSU or by outside providers for consultation regarding appropriateness for referral to the PCSK9i clinic. During the initial PCSK9i visit, a clinical pharmacist and a physician assistant performed a medical history and physical exam that included detailed documentation of current medications, past lipid-lowering therapies (allopathic and naturopathic), reported intolerances or side effects, diagnoses of lipid disorders using insurance-guided documentation requirements, instruction on injection technique, and a prescription for the PCSK9i medication in appropriately selected patients. The PCSK9i prescription was sent to

our specialty pharmacy to process and initiate an electronic prior authorization (PA), which was then completed by either the physician assistant or clinical pharmacist. Once approved, the PCSK9i prescription was routed to the preferred pharmacy and the clinical pharmacist followed up with the patient to review medication cost, injection technique, potential side effects, and timeline for follow-up lipid testing. Follow-up with the physician assistant was scheduled for 6 weeks (within 5 days from the 3rd injection), 6 months, and every 6 months thereafter. A blood sample was also collected before initiation of therapy (baseline). Measurement of plasma lipid and Lp(a) concentrations was performed as previously described.[19]

Statistical methods

Continuous measurements were summarized with means and standard deviations for normally distributed data and as medians and interquartile range (IQR) for non-normally distributed parameters. Categorical variables were summarized with counts and percentages. Time to approval and time to injection were compared across time intervals with a one-sided permutation test of the null hypothesis that median time did not change or increased vs. alternative hypothesis that median time decreased over the course of our 3-year experience. A two-factor repeated measures ANOVA was performed to test for differences in LDL and Lp(a) across dose/drug and time points.

Results

The cohort consists of 271 patients approved and actively treated with a PCSK9i. The average age was 61.8 years and the study population was equally divided between men and women (Table 1). Nearly half of the cohort (46%) had ASCVD as qualifying diagnosis, whereas FH alone or in combination with ASCVD made up the remaining indications (26% and 28%, respectively) (Table 1). Fifty-three percent of subjects in this cohort were deemed statin intolerant (unable to tolerate at least two statins, one at the lowest therapeutic daily dose). Among patients with FH, 46% were statin intolerant.

The approval rate for PCSK9i was 97% overall, with 29% of patients requiring at least one insurance appeal before approval. The median time to approval was 15 days, whereas the median time to first injection was 38 days. Both timelines were significantly reduced over the 3-year experience as the PCSK9i workflow was optimized (Table 5).

After insurance approval, the vast majority of patients successfully gained affordable access to PCSK9i, with only 2.3% unable to initiate or continue therapy due to cost (all of whom were Medicare patients). Among the entire cohort, the monthly average insurance co-pay was $235.93 (median $182.22, IQR $28.50, $374.75), but these were reduced to an average actual monthly patient out-of-pocket expense of $58.05 (median $0, IQR $0–8.30) due to some form of financial assistance (Table 2). For commercially insured patients, monthly average insurance co-pays were $221.65 (median $125), but these were reduced to a monthly patient out-of-pocket expense of $6.32 (median $0, IQR $0–5) with the use of a co-pay card (for which 74% of commercially insured patients qualified). Unfortunately, Medicare and Medicaid patients are prohibited from using co-pay cards. The only financial assistance programs available to Medicare patients are manufacturer-derived patient

assistance programs, such as Amgen Safety Net and Sanofi PASS programs.[20, 21] Medicare beneficiaries had an average insurance co-pay of $272.53 (median ($300, IQR $56–390), reduced to a patient out-of-pocket expense of $111.11 (median ($5, IQR $0–250) with use of patient assistance programs (10% of Medicare patients received PCSK9i free of charge) (Table 2). Finally, Medicaid insured patients had a co-pay and actual out-of-pocket expense of $6.05 (median $0, IQR $0–0) per month (Table 2). Within the entire cohort, 77% of patients paid less than $10 monthly for PCSK9i therapy. Two Veteran's Administration (VA) patients were excluded from the cost analysis given that all VA patients are required to have their prescriptions written by VA providers. .

Aggregated across product and dose, the median percent reduction in LDL-C and Lp(a) after 12 months of therapy were 60% and 23%, respectively (Table 3), consistent with results reported in controlled clinical trials.[4–6] It is noted that while LDL-C reduction reached maximum efficacy at 6 weeks, Lp(a) reduction was 12% at 6 weeks and reached maximum efficacy (25%) at 12 months. The incidence of reported adverse effects was low (Table 4). Musculoskeletal symptoms and injection site reactions were the most common side effects (8.1% and 5.9%, respectively). Twenty-eight percent of subjects reported at least one side effect at some point during PCSK9i therapy. However, only 5% of the cohort discontinued therapy due to adverse events (Table 4), whereas 2.3% of patients either discontinued or did not start therapy due to cost. The remaining 92.7% of patients successfully continued treatment throughout the duration of our assessment.

Discussion

We previously described the design of a dedicated PCSK9i clinic model to overcome the formidable challenges to access PCSK9i therapy for patients meeting FDA indications.[7] Here we shift the focus to the patient perspective, and in doing so highlight the value of our now established model for management of PCSK9i treatment. Overall, the implementation of a dedicated PCSK9i clinic has resulted in a 97% rate of drug approval, far higher than the national average approval rate of 40–50% reported in the literature.[9–12] Financial burden for patients was very reasonable in most cases, with an average monthly out-of-pocket expenditure of $57 and discontinuation rates due to cost of only 2.3%. This high approval rate and low patient out-of-pocket expenditure stands in contrast with media reports and the peer-reviewed literature in which about a third of patients were reported never filling PCSK9i prescriptions primarily due to cost.[10] Moreover, within our model, we noted dramatic improvements in time from initial visit to drug approval and time from initial visit to first injection, with median times of 44 days and 64.5 days prior to implementation of our program, dropping to current times of 15 days and 17 days, respectively. While this enhanced efficiency was partially due to the addition of dedicated personnel, it was largely accounted for by the adoption of a formalized and standardized evaluation process that ensured proper documentation of insurance criteria for coverage, transitioning from a paper to electronic format for insurance application, and, with time, improved understanding and communication with insurance companies in response to denials. Importantly, the observed improvement in time to medication approval was related to the process improvements that we implemented rather than a generalized relaxation in barriers to access, which only a few payers have adopted recently. While not directly assessed in this study, we anticipate that the

improved efficiency and access to PCSK9i translates into increased patient satisfaction and potentially improved clinical outcomes, as prior reports have highlighted increased risk of atherosclerotic events while high-risk patients await the lengthy approval process.[22]

Consistent with the clinical trial evidence, our real-world cohort recapitulates the LDL-C lowering efficacy and tolerability of the PCSK9i class. Interestingly, 53% of the patients in our PCSK9i cohort were completely statin intolerant. Three recent European cohorts also reported a ~50% rate of statin intolerance in patients referred for PCSK9i.[23–25] This is remarkable because it demonstrates that the availability of an official indication for statin intolerance (as granted by the European Medicines Agency) does not appear to influence the proportion of statin-intolerant patients receiving PCSK9i therapy. Interestingly, while LDL-C reduction reached peak efficacy by 6 weeks of therapy, Lp(a) reduction was 12% at 6 weeks and 25% at 12 months. This suggests that the Lp(a) lowering associated with PCSK9i is not simply mediated by LDL receptor upregulation.

As clinicians strive to optimize residual atherosclerotic risk reduction, our experience outlines an effective strategy to establish a PCSK9i clinic that efficiently improves patient access to affordable and highly efficacious treatment with PCSK9i. The keys to success in this PCSK9i clinic model are optimal staffing, appropriate patient identification, use of standardized protocols for data acquisition, continued pursuit of payer approval despite initial denials, and education of patients on cost-saving programs. We show that PCSK9i therapy is accessed easily and affordably by the majority of eligible patients, and that results from prospective clinical trials of PCSK9i on LDL and Lp(a) reduction are applicable to this real-world cohort.

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Table 1

Baseline Characteristics for the PCSK9 Inhibitor Therapy Cohort (N=271)	
Age (years +/− SD)	61.8 +/− 10.9
Gender	
Male, N (%)	135 (49.8%)
Female, N (%)	136 (50.2%)
Familial Hypercholesterolemia (FH), N (%)	147 (54%)
Without known ASCVD, N (%)	71 (26%)
With ASCVD, N (%)	76 (28%)
ASCVD* only (includes CAD), N (%)	124 (46%)
Asymptomatic ASCVD (CACS/CCTA/ICA), N (%)	42/200 (21%)
Mean CACS in Agatston units +/− SD	767.9 +/− 918.7
Median CACS in Agatston units (IQR)	496.9 (IQR 264.0–938.7)
Heart Transplant, N (%)	6 (2%)
LDL in mg/dl (Mean +/− SD)	
ALL (N=262)	141.1 +/− 56.5
ASCVD Only (N=121)	124.9 +/− 37.8
FH without known ASCVD (N=66)	167.6 +/− 78.5
FH + ASCVD (N=75)	143.7 +/− 49.6
Lipoprotein (a) in mg/dl (N=239)	
Mean +/− SD	67.10 +/− 76.5
Median (IQR)	37.0 (IQR 12.0–97.0)
Range	2.0–480.0
Current medication use at time of PCSK9i approval, N (%)	
High intensity statin	82 (30%)
Moderate intensity statin	29 (11%)
Low intensity statin	16 (6%)
Statin intolerant†	144 (53%)
Statin monotherapy	31 (11%)
Ezetimibe monotherapy	72 (27%)
Statin + ezetimibe	92 (35%)
BAS	33 (12%)

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Baseline Characteristics for the PCSK9 Inhibitor Therapy Cohort (N=271)	
Triple therapy ‡	26 (10%)
No prescription medications	67 (25%)
Supplemental therapy	48 (18%)

*Atherosclerotic Cardiovascular Disease (includes diagnosis of coronary artery disease by imaging as well)

†Unable to tolerate the lowest therapeutic daily dose

‡Triple Therapy = Statin + ezetimibe + bile acid sequestrant

ASCVD=Atherosclerotic Cardiovascular Disease; BAS=Bile Acid Sequestrantss; CACS=Coronary Artery Calcium Score; CAD=Coronary Artery Disease; CCTA=Coronary Computed Tomography Angiography; ICA=invasive coronary angiogram; IQR = interquartile range

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Table 2

Cost to Patient for PCSK9 Inhibitor Therapy				
	Overall	**Commercial Insurance**	**Medicare**	**Medicaid**
Percent of Patients, N (%)	269	119 (44%)	135 (50%)	15 (6%)
Insurance Co-pay ($)				
Average (+/− SD)	$235.93 (+/− 248.52)	$221.65 (+/− 276.49)	$272.53 (+/−221.39)	$6.05 (+/− 20.74)
Median (IQR)	$182.22 (28.50, 374.75)	$125 (30, 300)	$300 (56.37, 390)	$0 (0, 0)
Range	$0–1170	$0–1170	$0–1150	$0–75
Patient Out of Pocket Expense ($)				
Average (+/− SD)	$58.05 (+/− 135.17)	$6.32 (+/− 35.45)	$111.11 (+/− 174.22)	$6.05 (+/− 20.74)
Median (IQR)	$0 (0, 8.30)	$0 (0, 5)	$5 (0, 250)	$0 (0, 0)
Range	$0–1150	$0–100	$0–1150	$0–75
Using Co-pay card (%)		74%	N/A	N/A
Financial Assistance program, N (%)	54, (20%)	4, (3%)	46, (34%)	--
Unable to start or continue due to cost	2.3% (all Medicare)			

N/A = Not applicable

IQR = interquartile range; SD = standard deviation

Table 3

LDL-C Lowering after PCSK9 Inhibitor Therapy			
	% Change after 3rd injection	**% Change after 6 months**	**% Change after 1 year**
Alirocumab 75mg			
Median (IQR)	−52% (−39, −62)	−59% (−47, −72)	−56% (−46, −68)
Alirocumab 150mg			
Median (IQR)	−49% (−46, −57)	−55% (−40, −72)	−53% (−44, −68)
Evolocumab 140mg			
Median (IQR)	−65% (−50, −78)	−64% (−49, −78)	−61% (−54, −67)
Overall			
Median (IQR)	−57% (−45, −71)	−61% (−48, −75)	−60% (−48, −75)
Lipoprotein (a) Lowering after PCSK9 Inhibitor Therapy			
	% Change after 3rd injection	**% Change after 6 months**	**% Change after 1 year**
Alirocumab 75mg			
Median (IQR)	−12% (0, −27)	−23% (−12, −40)	−25% (−13, −39)
Alirocumab 150mg			
Median (IQR)	−12% (−9, −16)	−15% (−9, −21)	−18% (−12, −25)
Evolocumab 140mg			
Median (IQR)	−14% (0, −31)	−25% (−11, −43)	−18% (0, −35)
Overall			
Median (IQR)	−13% (0, −29)	−23% (−10, −38)	−23% (−9, −38)

Patients were excluded from this analysis if they changed from one PCSK9 inhibitor to another

IQR = interquartile range

Table 4

Side-Effects Reported at Least Once During PCSK9 Inhibitor Treatment(N=271)	
Musculoskeletal symptoms	22 (8.1%)
Injection site reactions	16 (5.9%)
Problems with Injection Technique	15 (5.6%)
Flu-like Symptoms	15 (5.5%)
Fatigue	9 (3.3%)
Nasopharyngitis	8 (3.0%)
GI Symptoms	5 (1.8%)
Headache	5 (1.8%)
Cognitive Issues	4 (1.5%)
Dizziness	3 (1.1%)
Erectile dysfunction	2 (0.7%)
Depression	2 (0.7%)
Hot Flashes	1 (0.4%)
Discontinuation rates due to side effects	13 (5%)

* Of the 13 patients who discontinued therapy due to side effects, the reasons cited were: myalgias (4); flu-like symptoms (3); cognitive issues (2); depression (1); fatigue (1); diarrhea (1); dermatologic (1)

Table 5

Time to Approval of PCSK9 Inhibitors				
	n	**Visit with provider to receipt of approval letter (days)**		
Clinical team Members		**Average time (+/− SD)**	**Median (IQR)**	**Range**
RN and Physician	81	56.1 (+/− 47.6)	44 (18, 78)	4–196
APP, Clinical Pharmacist and MA*	138	19.9 (+/− 23.4)	12 (7, 23.75)	0–151
APP, Clinical Pharmacist, MA and specialty pharmacy services†	26	8 (+/− 9.3)	6 (2.5, 7)	1–35
Overall	245	30.6 (+/− 37.3)	15 (7, 35)	0–196
Time to First Injection of PCSK9 Medications				
		Visit with provider to first injection (days)		
Clinical team Members		**Average time (+/− SD)**	**Median (IQR)**	**Range**
RN only	92	75.4 (+/− 54.1)	64.5 (35.75, 94.5)	14–319
APP, Clinical Pharmacist and MA*	134	45.4 (+/− 55.8)	31 (22, 49.75)	8–557
APP, Clinical Pharmacist, MA and specialty pharmacy services‡	17	22.4 (+/− 19.0)	17 (8, 29)	3–70
Overall	243	55.2 (+/− 55.8)	38 (24, 68.5)	3–557

APP = advanced practice provider; IQR = interquartile range; MA = medical assistant; RN = registered nurse; SD = standard deviation

*P<0.001 vs RN only

†P<0.001 vs APP, Clinical Pharmacist, MA

‡P=0.0016 vs APP, Clinical Pharmacist, MA