A Pharmacist-Run Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor Clinic: Short-Term Results and Practical Strategies

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BACKGROUND

- Cardiovascular (CV) disease is the number one cause of death within the United States and accounts for 30.8% of deaths within the United States, based on 2013 mortality data[1]
- Despite efforts to lower low-density lipoprotein cholesterol (LDL-C) and additional atherogenic cholesterol, many patients fail to achieve desirable lipid parameters[2,3]
- PCSK9 inhibitors (PCSK9i) offer another approach to lower LDL-C, especially in patients at high risk for future atherosclerotic cardiovascular events[4,5,10]
- Alirocumab (Praluent®) and evolocumab (Repatha®) work by promoting low-density lipoprotein receptor (LDL-R) recycling and increased cholesterol removal through inhibition of the chaperone protein, PCSK9, as illustrated in **Figure 1**[6,7]
- There are no CV outcomes data with PCSK9i, although clinical trials are underway

  ALIROCUMAB - ODYSSEY (NCT01663402)
  BOCOCIZUMAB - SPIRE-1 (NCT01975389) and SPIRE-2 (NCT01975376)
  EVOLOCUMAB - FOURIER (NCT01764633)

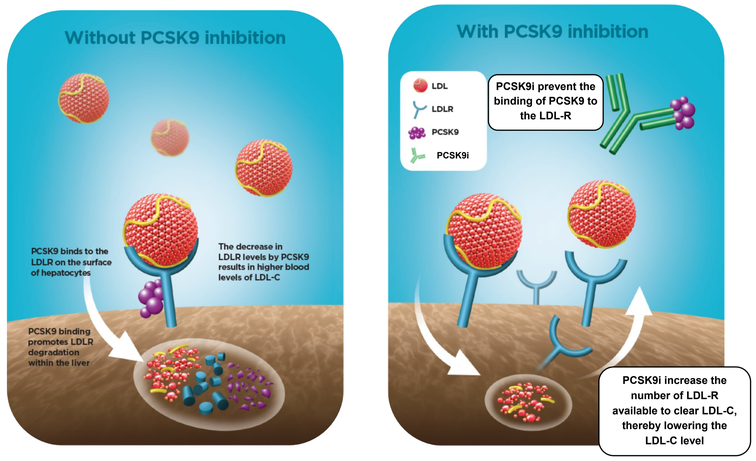

Figure 1: Alirocumab and evolocumab are fully human monoclonal antibodies that bind to PCSK9. Consequently, LDL-R recycling within a hepatocyte increases, promoting LDL-C removal from circulation.[6,7]
Image: Reference 8

PURPOSE

The objectives of this research are to report the real-world efficacy and safety of PCSK9i and share clinical managed care pearls from a pharmacist-run PCSK9i clinic.

METHODS AND STATISTICAL ANALYSIS

This is a prospective, observational, Institutional Review Board-approved study from an endocrinology practice involving patients referred to a pharmacist-managed PCSK9 inhibitor clinic. Upon referral, the following data were collected: patient demographic information, indication for referral, history of prior antilipemic therapy, notably statin use, and adverse medication-related events to previous therapies. The only exclusion criteria for this research was if a patient was deemed to not be an appropriate candidate for a PCSK9i, which was addressed with the referring provider.

Either alirocumab 75 mg or evolocumab 140 mg was initiated once every two weeks. Following the initiation of PCSK9i therapy, the pharmacist called each patient two weeks after the commencement of therapy as a reminder to administer the second dose. Follow-up labs were obtained four weeks after initiation of therapy.

This study assessed the efficacy [percent change from baseline in total cholesterol (TC), LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG)] and tolerability [via reported adverse events] of alirocumab and evolocumab. Paired t-tests were performed to compare baseline data to that at follow-up. P-values less than 0.05 were considered to be statistically significant.

The pharmacist investigated formulary coverage, initiated prior authorization requests, generated appeal requests (internal and external) and followed through to ensure each patient prescribed a PCSK9i had received the medication from a specialty pharmacy or found an alternative, financially sustainable way to obtain the medication (e.g., manufacture-sponsored programs, independent patient assistance programs, samples).

RESULTS

Demographics	Overall (N = 65)	Alirocumab (n = 35)	Evolocumab (n = 30)
Mean Age, Years [SD]	67 [9]	68 [9]	66 [9]
Mean Baseline Body Mass Index, kg/m^2 [SD]	33 [7]	33 [6]	33 [8]
Mean Baseline Weight, Pounds [SD]	207 [49]	213 [47]	200 [51]
Gender, n (%)			
Female	30 (46)	14 (40)	16 (53)
Male	35 (54)	21 (60)	14 (47)
Race, n (%)			
African American	3 (5)	2 (6)	1 (3)
Asian	0 (0)	0 (0)	0 (0)
Hispanic	0 (0)	0 (0)	0 (0)
White	60 (92)	31 (89)	29 (97)
Unknown	2 (3)	2 (6)	0 (0)
Atherosclerotic Cardiovascular Disease Present, n (%)	51 (78)	30 (86)	21 (70)
Familial Hypercholesterolemia, n (%)	13 (20)	7 (20)	6 (20)
Receiving a Statin at Baseline, n (%)	36 (55)	25 (71)	11 (37)
Type 1 Diabetes Mellitus, n (%)	7 (11)	4 (11)	3 (10)
Type 2 Diabetes Mellitus, n (%)	43 (66)	25 (71)	18 (60)

Table 1: Baseline demographics of patients referred to the pharmacist-managed PCSK9 inhibitor clinic
Abbreviation: SD - standard deviation

Lipid Parameter	A Baseline Lab Data ± Standard Deviation (mg/dL)		
	Overall (N = 65)	Alirocumab (n = 35)	Evolocumab (n = 30)
Total Cholesterol	223 ± 69	220 ± 77	226 ± 59
LDL-C	136 ± 59	133 ± 66	139 ± 50
Non-HDL-C	173 ± 67	169 ± 74	177 ± 59
HDL-C	50 ± 14	51 ± 15	49 ± 13
Triglycerides	212 ± 140	204 ± 112	221 ± 169

Lipid Parameter	B Initial Follow-Up Lab Data ± Standard Deviation (mg/dL)			Overall Percent Change from Baseline ± SD
	Overall (N = 59)	Alirocumab (n = 33)	Evolocumab (n = 26)	
Total Cholesterol	142 ± 50	143 ± 53	140 ± 47	-36%
LDL-C	59 ± 40	60 ± 43	59 ± 38	-57%
Non-HDL-C	88 ± 47	88 ± 52	87 ± 43	-49%
HDL-C	54 ± 17	54 ± 19	53 ± 15	+8%
Triglycerides	143 ± 63	143 ± 72	143 ± 51	-33%

Tables 2A and 2B: Baseline lipid data reflect that of the entire cohort (**Table 2A**) and four-week follow-up data for those who received two doses of a PCSK9i and returned for repeat labs (**Table 2B**)
Abbreviations: HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; SD - standard deviation

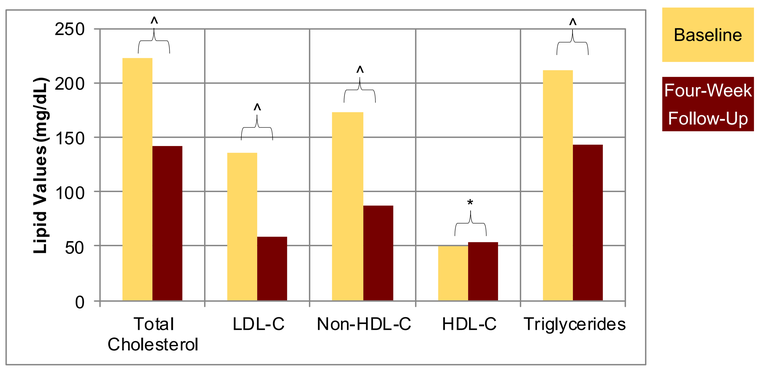

Figure 1: Baseline and follow-up lipid data after four weeks of PCSK9i therapy. The percent change from baseline improved significantly for all lipid parameters.
* $p < 0.05$; ^ $p < 0.001$
Abbreviations: HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol

SAFETY

- **Eighteen patients (28%) reported side effects they thought were related to their PCSK9i**
  - The most commonly reported side effect was a runny nose / sinusitis (n = 8 [12%])
  - Only 7 patients (11%) discontinued therapy secondary to a side effect(s), which included: abdominal pain, dysuria, fatigue, injection site pain, insomnia, muscle weakness/soreness, muscle tremors, runny nose / sinusitis and vertigo

MANAGED CARE

Outcome	Overall (N = 65)	Alirocumab (n = 35)	Evolocumab (n = 30)
Approval, n (%)	34 (52)	20 (57)	14 (47)
Denial, n (%)	18 (28)	8 (23)	10 (33)
Other*, n (%)	13 (20)	7 (20)	6 (20)

Figure 2: Managed care status for PCSK9i requests.
* The outcome, "other," reflects patients who are completing their four-week trial with a PCSK9i (n = 2), those whose request is pending review by managed care (n = 2), those who discontinued therapy secondary to adverse effects (n = 5), those where it is unclear what the patient's insurance plan is (n = 1) or those who are receiving medication through alternative means [e.g., manufacture-sponsored programs, samples] (n = 3).

CLINICAL PEARLS AND PRACTICAL MANAGED CARE STRATEGIES

- Are you goal driven or dose driven? The most recent consensus lipid management guidelines recommend the use of atherogenic cholesterol goals[9] and acknowledge the use of PCSK9i,[4] as do other disease state management guidelines.[5,10]
- Assess the need for a PCSK9i. Is your patient on a statin and has the dose been maximized or switched to a more potent statin? Will ezetimibe achieve the desired atherogenic cholesterol goals based on patient-risk category?
- Data mine and capture all relevant clinical information to disseminate to managed care, which may include: any documented atherosclerotic cardiovascular disease, risk equivalents, antilipemic intolerances and dose(s), notably statins.
- Consider requesting samples from the manufacture and completing a one-month trial to demonstrate your patient's response to therapy before submitting a request to managed care. Then use this information, in addition to relevant clinical information, to further support your rationale.
- Frequently, we found managed care rejecting our requests because patients were not receiving statin therapy, as they were intolerant to multiple statins; this was termed "off label." These patients' maximally tolerated dose of statin therapy was zero milligrams. The labeling for both agents is nebulous and does not indicate a patient has to be receiving a statin.[6,7]

CONCLUSIONS

Analysis of this observational, real-world data suggest that PCSK9i are associated with significant, intensive and predictable reductions in atherogenic cholesterol, as demonstrated in previously reported clinical trials. Importantly, the use of this class of medications demonstrated a significant reduction in both LDL-C and non-HDL-C, -57% and -49% ($p < 0.001$), respectively, each of which are considered to be atherogenic and primary targets for antilipemic therapy.[9] Overall, PCSK9i were well tolerated and associated with a low rate of discontinuation. These results suggest that PCSK9i may be a viable option for patients not at goal despite the use of first-line agents (i.e., statins) or for patients intolerant to multiple first line therapies; they offer a novel, efficacious and potentially safe approach to significantly lower atherogenic cholesterol in patients with an increased risk for CV events. Although there are many managed care obstacles to overcome, the use of a pharmacist was associated with a high medication-approval rate. Limitations of this study included the small sample size and observational design.

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DISCLOSURES

Dr. Robert S. Busch serves on the Speakers Bureau for Amgen, Inc. and Regeneron Pharmaceuticals, manufacturers of Repatha® and Praluent®. Drs. Stryker, Kane and Hamilton have nothing to disclose.