Anti PCSK9 Monoclonal Antibody Treatment in Elderly Patients: A Real-world Clinical Experience

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ABSTRACT **Background:** The use of proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs) is emerging for lowering low-density lipoprotein cholesterol (LDL-C). However, real-world data is lacking for their use among elderly patients.

Objective: To define the characteristics of elderly patients treated with PCSK9 mAbs and to evaluate the efficacy and tolerability compared with younger patients.

Methods: We conducted a retrospective cohort study of elderly patients (≥ 75 years at enrollment) treated with PCSK9 mAbs for primary and secondary cardiovascular prevention. Data were retrieved for demographic and clinical characteristics; indications for treatment; agents and dosages; concomitant lipid lowering treatment; LDL-C levels at baseline, 6, 12 months, and at the end of follow up. Data also included achieving LDL-C target levels and adverse effects.

Results: The cohort included 91 elderly patients and 92 younger patients, mean age 75.2 ± 3.76 and 58.9 ± 7.4 years (P < 0.0001). Most patients (82%, 80%) were in high/very high-risk categories. For almost all (98%, 99%), the indication was statin intolerance, with PCSK9 mAb monotherapy the most prevalent regimen. The average follow-up was 38.1 ± 20.5 and 30.9 ± 15.8 months (P = 0.0258). Within 6 months the LDL-C levels were reduced by 57% in the elderly group and by 59% in the control group (P = 0.2371). Only 53% and 57% reached their LDL-C target levels. No clinically significant side effects were documented.

Conclusion: PCSK9 mAbs have similar effects and are well tolerated among elderly patients as in younger patients.

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KEY WORDS: elderly, low-density lipoprotein cholesterol (LDL-C), proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs), statins

Dyslipidemia is a well-established major risk factor for cardiovascular disease, which is the main cause of death worldwide. Furthermore, trials of low-density lipoprotein cholesterol (LDL-C) lowering indicate that the relative risk reduction of cardiovascular events and cardiovascular death is proportional to the absolute reduction in low-density lipoprotein cholesterol LDL-C plasma levels, independent of the means of reduction, with no known evidence for lower LDL-C level limit [1,2].

Accordingly, current guidelines recommend statin treatment for patients at high cardiovascular risk or with established cardiovascular disease to prevent major cardiovascular events by lowering of atherogenic lipoproteins [3,4]. The existing LDL-C lowering agents, such as statins and ezetimibe, significantly reduce the LDL-C levels and have a dramatic impact on the cardiovascular morbidity and mortality [5]. However, frequent perceived concern of statin use is muscle-related complaints, which may limit their use by intolerability.

In the past decade, a novel class of drugs has emerged. Anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs) block the PCSK9 protein and by that method elevate the number of LDL receptors on the hepatocytes surface. In clinical trials, the approved agents, alirocumab and evolocumab, either alone or in combination with statins and/or ezetimibe significantly reduced the LDL-C levels by approximately 60%, while cardiovascular outcomes trials demonstrated a significant reduction of events with their use, alongside a good tolerability and safety profile [5-7].

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial showed reduced LDL-C levels and indicated that PCSK9 was well tolerated. The continued use of evolocumab over 8 years showed consistently low rates

of adverse events, which did not exceed those observed initially in the placebo group during the original study. Moreover, this long-term treatment led to additional reductions in cardiovascular events when compared to delayed treatment initiation [8-11]. However, current recommendations for PCSK9 mAbs therapy are not age-specific, reflecting the rather paucity of evidence obtained among elderly population as those for individuals younger than 75 years of age [3,4].

The aims of the study were to define the characteristics of elderly patients treated with PCSK9 mAbs in real-world settings and to evaluate the efficacy and tolerability compared with younger patients. We assessed demographic and clinical characteristics, indications for treatment, efficacy, and tolerability.

PATIENTS AND METHODS

We conducted a single-center retrospective study, which included patients treated at two lipids and preventive cardiology clinics at Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel. Patients were included if they were started on PCSK9 mAbs treatment with either evolucumab or alirocumab between 1 January 2015 and 1 January 2021. Patients with missing data were excluded. Patients were categorized into two age groups: elderly (defined as 75 years or older) and a control group composed of patients younger than 74 years of age, which were chosen according to the base line characteristics of the study group.

The following parameters were extracted from the electronic medical records and were evaluated for the two groups: demographic parameters (age, sex); co-morbidities (ischemic heart disease, diabetes mellitus, hypertension, peripheral artery disease, previous stroke, renal failure, current smoking); cardiovascular risk level, and LDL-C target levels according the 2019 ESC/EAS guidelines [3] (high risk: LDL-C < 70 mg/dl, very high risk: < 55 mg/dl), an indication for PCSK9 mAbs (not achieving target level at maximally tolerated statin dose and ezetimibe or statins intolerance), concomitant lipid lowering treatment, PCSK9 mAbs agent and dosage (alirocumab/evolocumab), treatment duration (from starting the treatment until 28 February 2022), baseline and follow up LDL-C levels (6 and 12 months ± 1 month and at the end of follow-up), alirocumab dose changes, and documented side effects.

Table 1. Baseline characteristics

Baseline variable	All, N (%)	> 75 years	< 75 years	*P*-value
All patients, n (% of total)	183 (100)	91 (49.7)	92 (50.3)	
Sex (female)	93 (50.8)	50 (53.7)	43 (46.3)	0.30
Age in years, median (IQR)	69.0 (61.0–75.0)	75.0 (75.0–78.0)	61.0 (55.0-64.0)	
Cardiovascular risk factors				
Diabetes mellitus	87 (47.5%)	35 (38.5%)	52 (56.5%)	0.02
Hypertension	136 (74.3%)	76 (83.5%)	60 (65.5%)	0.006
IHD	137 (74.8%)	70(76.9%)	67 (72.8%)	0.61
Ischemic stroke or TIA	15(8.2%)	14 (15.4%)	1 (1.1%)	0.001
Active smoking	35 (19.1%)	15 (16.5%)	20 (21.7%)	0.45
CKD	20 (10.9%)	12(13.2%%)	8 (8.7%)	0.35
PVD	43(23.5%)	33 (36.2%)	10 (10.8%)	0.001
Risk				0.85
High	34 (18.6%)	16 (17.6%)	18 (19.6%)	
Very high	149 (81.4%)	75 (82.4%)	74 (80.4%)	
Indication				0.62
Statin intolerance	180 (98.4%)	89 (97.8%)	91 (98.9%)	
LDL-C levels not achieved	3(1.6%)	2 (2.2%)	1 (1.1%)	
LDL-C at baseline, mean ± standard deviation	153.7 (123.0–177.0)	153.2 (126.0–177.0)	154.1 (120.5–177.5)	0.76

CKD = chronic kidney disease, IHD = ischemic heart disease, IQR = interquartile range, PVD = peripheral vascular disease, TIA= transient ischemic attack

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous data was expressed as mean ± standard deviation or as median and interquartile range (25–75 percentile), as appropriate. Results were compared using *t*-test. Chi-square was used for comparing dichotomous variables.

RESULTS

The cohort included 183 patients, 91 in the elderly group (mean age 75.2 ± 3.76 years) and 92 in the control group (58.9 ± 7.4 years), without significant difference in sex (55% women vs. 47% men, respectively $P = 0.3$). Demographics and clinical characteristics are shown in Table 1. Prevalence of ischemic heart disease was similar between the groups (77% among the elderly vs. 72.8% among the younger patients, $P = 0.61$). Diabetes mellitus was more common in the control group (56.5% vs. 38.5%, $P = 0.02$) and hypertension was more common among the elderly group (83.5% vs. 65.5%, $P = 0.006$, respectively).

Most patients were in the very-high cardiovascular risk category (82.4% and 80.4%, respectively). The indication for PCSK9 mAbs treatment was statin intolerance in most cases (97.8% and 98.9% in the elderly group and control group, $P = 0.621$, respectively). Average follow-up was 38.1 ± 20.5 months in the elderly group and 30.9 ± 15.8 months in the control group ($P = 0.0258$).

PCSK9 mAbs was prescribed as a monotherapy among most patients (72.5% and 81.5% in the elderly group and control group, $P = 0.249$, respectively). Alirocumab was used more frequently; however, it did not reach statistical significance (64.8% and 59.8%, $P = 0.543$). Alirocumab 75 mg dosage was initially used in 57.9% in the elderly and 42.1% in the control group, respectively ($P = 0.262$), Dose was increased to 150 mg in 10 patients (9.6%) of the elderly group vs. only 1 patient (1.8%) in the control group, $P = 0.005$.

Concomitant statin therapy was prescribed for 9 patients (9.9%) of the elderly group and 12 (13.0%) for the control group ($P = 0.64$). Ezetimibe was used by 18 elderly patients (19.8%) and by 9 (9.8%) in the control group ($P = 0.06$) [Table 2].

Baseline LDL-C levels were comparable between the groups (153.19 ± 35.39 and 154.14 ± 46.21 mg/dl, $P = 0.766$, respectively]. Within 6 months LDL-C levels were similarly reduced to 65.9 ± 28.5 mg/dl (-57%) and to 63.8 ± 38.0 mg/dl (-59%), $P = 0.2371$ and 0.359, respectively, and

Table 2. Treatment characteristics of PCSK9 mAbs therapy according age groups

Characteristic	All	> 75 years	< 75 years	*P*-value
Anti-PCSK9 monoclonal Ab				
Alirocumab, n (%)	114 (62.3%)	59 (64.8%)	55 (59.8%)	
Initial dose: 75 mg	57 (50.0%)	33 (57.9%)	24 (42.1%)	
150 mg	58 (50.8%)	27 (46.5%)	31 (53.4%)	0.54
Dose increased during follow-up, n (%)	11 (9.6%)	10 (16.9%)	1 (1.8%)	
Evolocumab, n (%)	69 (37.7%)	32 (35.2%)	37 (40.2%)	
Concomitant lipid lowering agents (statin), n (%)	21 (11.5%)	9 (9.9%)	12 (13.0%)	0.64
Ezetimibe, n (%)	27 (14.7%)	18 (19.8%)	9 (9.8%)	0.06

PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies

Table 3. Results of PCSK9 mAbs therapy according age groups

Therapy	All	> 75 years	< 75 years	*P*-value
LDL-C at 6 months, mg/dl, mean ± SD	64.9 (43.0–82.0)	65.9 (43.0–83.0)	63.8 (43.0–78.5)	0.23
Percentage of reduction, mean ± SD	58.0 (47.0–69.4)	56.9 (45.4–69.0)	59.1 (50.0–70.5)	0.35
LDL-C at 12 mg/dl months, mean ± SD	62.1 (40.0–79.0)	65.7 (44.0–88.0)	58.7 (37.5–74.5)	0.05
LDL-C target reached, n (%)	100 (54.6)	48 (52.7)	52 (56.2)	0.65
Adverse events, n (%)	8 (4.4)	8 (100)	0	0.003

LDL-C = low-density lipoprotein cholesterol, PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies, SD = standard deviation

maintained stable until the end of follow up period (65.7 ± 28.2 and 58.7 ± 29.4 mg/dl, $P = 0.059$, respectively).

Only 53% of the patients in the elderly group and 56% in the control group reached their LDL-C target levels ($P = 0.65$) [Table 3, Figure 1].

Side effects were reported in 8.8% (n=8) of the elderly group, with myalgia being the most reported adverse reaction. No adverse effects were reported among the control group. Four patients among the elderly group died during the follow-up period, with no clinical relation to the PCSK9 mAbs treatment.

Among the elderly group, 7 patients (7.7%) were non-adherent to PCSK9 mAbs compared with 6 (6.5%) among the control group, mostly due to compliance concerns.

DISCUSSION

This study was a real-world practice study. To the best of our knowledge, it is the first to be conducted specifically on an elderly population. It demonstrates that among elderly patients, the major indication for treatment with anti PCSK9 mAbs is statin intolerance, and most patients use it as a single agent. The efficacy of these agents is comparable in both elderly and young patients, with better tolerability among younger patients.

While cholesterol lowering has been proven to be essential for prevention and reduction of cardiovascular risk in a wide range of individuals [12], the general misleading perception is that LDL-C reduction may not be as applicable in the older population. In patients above age 75 years, physicians should consider issues like frailty and life expectancy. In frail patients or those with a shorter life expectancy, avoiding cholesterol-lowering therapies should be considered. Moreover, older patients are often not likely to receive adequate (or intensive) lipid lowering treatment, frequently due to undesired side-effects, in particular muscle-related effects of statins, as well as perceived concerns about polypharmacy and potential drug interactions [13].

The clinical benefit of LDL-C reduction in older adults remains debated. Some trials have reported diminished efficacy for statins in the elderly. Few trials are specifically designed to include elderly people, which contributes to the therapeutic uncertainty concerning the risk-benefit balance with intensive LCL-C lowering in this population.

In the FOURIER study, there were small variations in the cardiovascular event rate across the age range (for the primary endpoint, Kaplan-Meier at 3 years 15.6%, > 69 years, vs. 15.1%, ≤ 56 years, $P = 0.45$); however, the relative efficacy of evolocumab was consistent regardless of patient age (for the primary endpoint Q1: hazard ratio [HR] 0.83, 95% confidence interval [95%CI] 0.72–0.96; Q2: HR 0.88, 95%CI 0.76–1.01; Q3: HR 0.82, 95%CI 0.71–0.95; Q4: HR 0.86, 95%CI 0.74–1.00; $P_{interaction} = 0.91$) and the key secondary endpoint (cardiovascular death, myocardial infarction, stroke Q1: HR 0.74, 95%CI 0.61–0.89, Q2: HR 0.83, 95%CI 0.69–1.00; Q3: HR 0.78, 95%CI 0.65–0.94; Q4: HR 0.82, 95%CI 0.69–0.98; $P_{interaction} = 0.81$) [9].

In a pooled analysis from 10 trials, alirocumab led to substantial LDL-C reductions in every age group, and 305 patients (6.1%) were aged ≥ 75 years [11].

Although statin therapy reduces the risk of vascular mortality and major coronary events irrespective of age, the evidence is weaker in patients over 75 years [9,11,13]. Overall, statin therapy compared with a placebo or more intensive statin therapy compared with less intensive statin therapy reduced the risk of major coronary events, but there appeared to be a trend toward slighter proportional risk reductions with increasing age. Absolute risk reduction, however, increases with advancing age [13]. However, a meta-analysis explored the effectiveness of statin therapy across many age categories, including patients aged 75 years and older [14]. These results reinforce the guidelines recommendations for the use of lipid-lowering therapies, including non-statin treatment, in older patients [3].

The indication for PCSK9 mAbs use in most of our patients was statin intolerance. This finding is consistent with other similar real-world reports [15,16]. As a result, most of our patients, like those in other real-life reports (63% by Zafrir et al. [16], 70.2% by Bradley et al. [17]), were treated by PCSK9 mAbs as a single lipid lowering agent. Nevertheless, sub-analysis of the ODYSSEY OUTCOMES study revealed that alirocumab reduced the relative risk of major adverse cardiovascular events irrespective of background statin treatment, with high efficacy among the PCSK9 mAb monotherapy group [18].

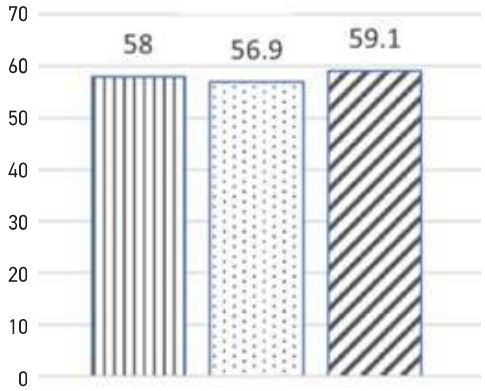
The inhibition of PCSK9 is associated with substantially reduced LDL-C levels [13]. Previous randomized controlled studies reported a 50–60% sustained reduction in the LDL-C levels with PCSK9 mAbs treatment [6,7], while real-world data showed a similar effect [13-15]. Our study results also demonstrated that older adults indeed experienced a dramatic LDL-C level reduction with PCSK9 mAbs agents as seen with younger population. These results were stable with the follow-up period among adherent patients, similar to reports from previous studies [15].

Even though 53% of elderly patients attained their target LDL-C levels, only 17% had a dose increase of alirocumab during the follow-up (50% initially received

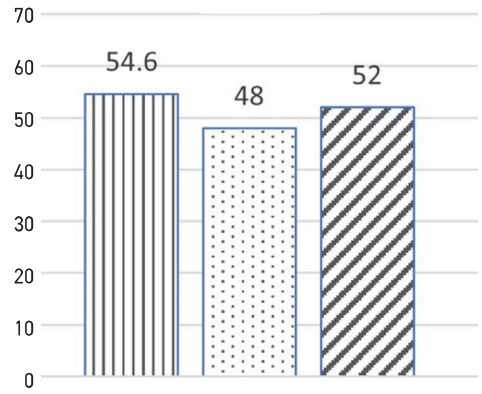
Figure 1. LDL reduction and target LDL-C reached (%) at baseline, 6, and 12 months of follow-up, according to groups

LDL-C = low-density lipoprotein cholesterol
(vertical lines = total, dots ≥75 years, diagonal lines < 75 years)

[A] Percentage of reduction, % mean ± standard deviation, $P = 0.35$



[B] LDL-C target reached, n (%)



the lower dose) and only 15% were prescribed ezetimibe. These observations reflect real-world clinical practices and emphasize the need for improvement in the future.

In the phase 3 major cardiovascular outcomes PCSK9 mAbs studies, the ODYSSEY OUTCOMES trial and the FOURIER study demonstrated no interaction between age and the impact of treatment on the primary endpoint (65-year cut-off: 27% of the population in ODYSSEY OUTCOMES and 44% of those in the FOURIER) [6,7].

A sub analysis of the ODYSSEY OUTCOMES study showed that the beneficial effect of alirocumab was independent of age and without significant safety issues in 5084 patients (26.9%) ≥ 65 years. However, only 1007 patients (5.3%) were ≥ 75 years and 42 (0.2%) ≥ 85 years [13]. In addition, another sub-analysis of this study disclosed that alirocumab decreased the risk of any stroke (HR 0.72, 95%CI 0.57–0.91) and ischemic stroke (HR 0.73, 95%CI 0.57–0.93) without increasing hemorrhagic stroke (HR 0.83, 95%CI 0.42–1.65) [19]. As primary treatment goals in older patients should maintain or improve quality of life, prevention of strokes is import as stroke can lead to limitations in functional capacity and cognitive function and to a significant impairment in quality of life [20].

Zafrir and colleagues [15] reported 10% side effects in similar Israeli cohort, which was consistent with our findings among the elderly patients. In both studies, the adverse events were mainly myalgia and musculoskeletal pain. Nevertheless, in a sub-analysis of the ODYSSEY trial, Sinnaeve and co-authors [13] found that although more musculoskeletal side effects were reported in the elderly group treated with alirocumab compared with younger patients, the same difference was seen between elderly and control placebo-treated groups. The musculoskeletal complaints seen in our study were probably age-related and not specific to the PCSK9 mAbs treatment.

The strength of this study is it reflects real-world practice. Its limitations are its retrospective design, single center, and relatively small study groups, unpowered to present cardiovascular outcomes.

CONCLUSIONS

In a real-world setting, PCSK9 mAbs have similar effects and are well tolerated among elderly patients as in younger patients. Further studies are needed to clarify these findings in a larger elderly population as well as the effect on cardiovascular outcomes.

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Capsule

DNA hide-and-seek

Liquid biopsy for tumor analysis offers the potential for noninvasive access using a blood draw instead of a surgical procedure. In addition, sampling the blood can detect tumor DNA even when the location of a tumor is unknown. However, circulating tumor DNA is usually scarce, and it can be difficult to collect enough blood for adequate detection, especially in cases where tumors are small. **Martin-Alonso** and colleagues addressed this difficulty by developing two different types of priming agents that protect circulating DNA from destruction. With these agents, more DNA remains in the bloodstream and is easier to detect even in small blood volumes. In mouse models of cancer, both approaches greatly increased the sensitivity of liquid biopsies.

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Capsule

Blood alterations in long COVID

Some individuals can endure persistent, debilitating symptoms for many months after an initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2-2) infection. However, the factors underpinning these health issues, called long COVID, are poorly understood. Comparing the blood of patients with confirmed SARS-CoV-2 infection with that of uninfected controls, **Cervia-Hasler** and co-authors found that patients experiencing long COVID exhibited changes to blood serum proteins indicating activation of the immune system's complement cascade, altered coagulation, and tissue injury. At the cellular level, long COVID was linked to aggregates comprising monocytes and platelets. These findings provide a resource of potential biomarkers for diagnosis and may inform directions for treatments.

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