

# Treatment with Anti-PCSK9 Monoclonal Ab: Experience from a Lipid Clinic in Israel

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## ABSTRACT

**Background:** There is an increasing use of anti-protein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs); however, real-world data is lacking.

**Objectives:** To define the demographic and clinical characteristics of patients treated with anti-PCSK9 mAbs. To evaluate efficacy, tolerability, and differences between the approved agents.

**Methods:** A retrospective cohort study was conducted of patients treated at the lipid clinic at Rabin Medical Center (Beilinson Campus), Israel, from January 2016 to December 2019. Data from electronic records were evaluated for demographic and clinical characteristics, indication for use, response of lowering low-density lipoprotein cholesterol (LDL-C)/non-high-density lipoprotein cholesterol (non-HDL-C) levels and reaching target levels, side effects, tolerability, differences between the agents, and doses.

**Results:** The study cohort included 115 patients. Two-thirds (n=75) were at high cardiovascular risk, the rest at very high risk (n=40). The major indication for treatment was statin intolerance (n=97, 84%). Most patients (n=102, 88%) were treated by anti-PCSK9 mAbs agents only. LDL-C and non-HDL-C levels were decreased by 47% and 39%, respectively (156 + 49 to 81 + 39 and 192 + 53 to 116 + 42 mg/dl), within 6 months and remained stable. Two-thirds (n=76) of the patients reached their lipid target levels. No clinically significant differences were observed between the agents in efficacy or tolerability.

**Conclusions:** In a real-world setting, anti-PCSK9 mAbs are used primarily as a single agent in high-risk and very high-risk cardiovascular populations with statin intolerance. They are well tolerated and effective in reduction of LDL-C levels. Further studies are needed to clarify comparisons between agents and doses.

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**KEY WORDS:** alirocumab, anti-PCSK9 monoclonal antibodies, evolocumab, lipid clinic, real world

The main pathological process of cardiovascular diseases (CVD) is atherosclerosis, largely due to an excess of low-density lipoprotein cholesterol (LDL-C). The available lipid lowering agents, statins, and ezetimibe significantly reduce the LDL-C levels and have a dramatic impact on the cardiovascular mortality and morbidity [1].

Recently, a new class of drugs, anti-protein convertase subtilisin/kexin type 9 (PCSK9) fully human monoclonal antibodies (mAbs), has become attainable. These agents are involved in controlling the level of the LDL receptor. In clinical trials, the approved agents, alirocumab and evolocumab, either alone or in combination with statins and/or ezetimibe have been shown to significantly reduce the LDL-C levels, on average by 60%. Cardiovascular outcome (CVO) trials documented significant reduction of various events with good tolerability [2–5].

In Israel anti-PCSK9 mAbs are indicated for high/very-high cardiovascular risk patients, who do not reach the LDL-C target levels on maximal tolerated statin and ezetimibe dosage. An approval from regulatory agents and copayment are required.

As the use of these agents is emerging, there is a need for real-world data concerning their indications, efficacy, and tolerability.

The aims of the study were to depict the demographic and clinical characteristics of patients under anti-PCSK9 mAbs treatment, to evaluate their response in terms of lowering LDL-C/non-high-density lipoprotein cholesterol (non-HDL-C) levels and reaching lipids target levels, and to document tolerability and any differences between the agents and doses.

## PATIENTS AND METHODS

A retrospective study was conducted, which included all patients treated at the lipid clinic at Rabin Medical Center (Beilinson Campus), Israel.

The inclusion criteria were treatment and follow-up at the clinic from 1 January 2016 and starting treatment with anti-PCSK9 mAbs before 31 December 2019. Patients with missing data were excluded from the cohort.

The following parameters were extracted from the electronic medical records and were evaluated: demographic parameters (age, sex)-co-morbidities (ischemic heart disease, diabetes mellitus, hypertension, peripheral artery disease, previous stroke,

renal failure, smoking), cardiovascular risk level, and LDL-C/non-HDL-C target levels according the 2016 ESC/EAS guidelines. The 2016 ESC/EAS guidelines include high-risk LDL-C < 100 mg/dl or non-HDL-C < 130 mg/dl and very high risk < 70 mg/dl and < 100 mg/dl, respectively [6]. The indication for anti-PCSK9 mAbs (not reaching target level at maximally tolerated statin dose and ezetimibe/statin intolerance), associated lipid lowering treatment, anti-PCSK9 mAbs agent and dosage (alirocumab / evolocumab), treatment duration (from starting the agent to 28 February 2020), baseline and follow-up LDL-C/non-HDL-C levels (6, 12, and 18 months  $\pm$  1 month), documented side effects, treatment discontinuation, alirocumab dose changes, as well as any differences between the two agents (efficacy, tolerability, compliance) were documented.

### STATISTICAL ANALYSIS

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

## RESULTS

The study cohort included 115 patients, median age was 68 years (IQR 63.5–73), 62% (n=71) were females. Two-thirds (n=75, 66%) were at high cardiovascular risk, while the rest at very high risk (n=40, 34%). Their co-morbidities are detailed in Table 1.

As the major indication for treatment with anti-PCSK9 mAbs was statin intolerance (n=97, 84%), most of the patients (n=102, 88%) were treated by anti-PCSK9 mAbs agents only. The median treatment and follow-up duration were 24 months (IQR 12–38).

Figure 1 presents the LDL-C and non-HDL-C levels along 18 months of follow-up. The levels were decreased by 47% and 39%, respectively ( $156 \pm 49$  to  $81 \pm 39$  and  $192 \pm 53$  to  $116 \pm 42$  mg/dl) within the first 6 months and remained stable along the entire period.

Two-thirds (66%, n=76) of patients reached their LDL-C/non-HDL-C target levels. Among the 75 high-risk patients, 64% (n=48) achieved their target levels (LDL-C < 100 mg/dl or non-HDL-C < 130 mg/dl), while 70% (n=28) of the 40 very high-risk group achieved their target levels (< 70 mg/dl and < 100 mg/dl, respectively). Of the 102 patients who were treated by anti-PCSK9 mAbs alone, 67% (n=68) reached their target levels.

Of the entire cohort, 77% (n=88) patients were treated by alirocumab (65 patients received 75 mg and 23 patients received 150 mg) and 23% (n=27) by evolocumab. No clinically significant differences concerning the characteristics, the indication for treatment, and concomitant lipid lowering agents was obtained between the groups (data not shown).

**Table 1.** Demographic and clinical characteristics of the study cohort (n=115)

Variable	Entire cohort (n=115)
Age, years, median (IQR)	68 (63.5–73)
Female sex, n (%)	71 (62%)
Treatment duration, median months (IQR)	24 (12–38)
<b>Cardiovascular risk</b>	
High risk, n (%)	75 (66%)
Very high risk, n (%)	40 (34%)
<b>Co-morbidities</b>	
Hypertension, n (%)	77 (67%)
Diabetes mellitus, n (%)	48 (42%)
Ischemic heart disease, n (%)	47 (41%)
Transient ischemic attack/cerebrovascular accident, n (%)	38 (33%)
Peripheral vascular disease, n (%)	31 (27%)
Smoking, n (%)	20 (17%)
Fatty Liver, n (%)	18 (16%)
Renal Failure, n (%)	7 (6%)
<b>Anti-PCSK9 mAbs indication</b>	
Statin intolerance, n (%)	97 (84%)
Not at target level on maximal tolerated dose with statin+/-ezetimibe, n (%)	18 (16%)
<b>Treatment</b>	
Anti-PCSK9 mAbs alone, n (%)	102 (88%)
Anti-PCSK9 mAbs with statin and ezetimibe, n (%)	8 (7%)
Anti-PCSK9 mAb with ezetimibe, n (%)	3 (3%)
Anti-PCSK9 mAbs with statin, n (%)	2 (2%)

anti-PCSK9 = anti-protein convertase subtilisin/kexin type 9 (PCSK9), IQR = interquartile range, mAbs = monoclonal antibodies

Figures 2A-2C show the LDL-C/non-HDL-C levels and percentage of change during the follow-up period for each agent. There was no clinically significant difference between them.

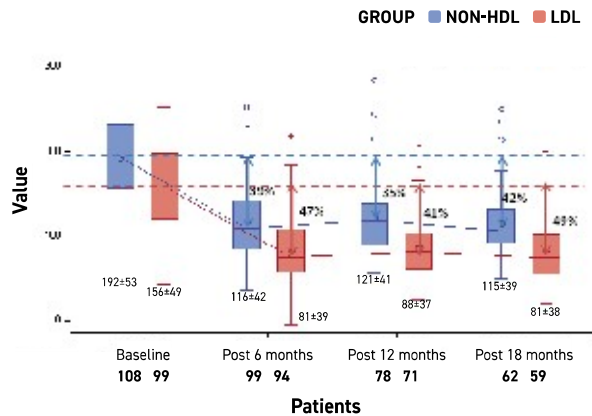
Overall, the agents were well tolerated 84% (n=97). The main side effect was myalgia in 6% (n=6). The dose of the alirocumab 75 mg was increased in 25 patients (38%), in none it was reduced. Three patients (3%) were changed from one agent to the other and the medication was stopped in another 7 (6%), all were treated by alirocumab. Ten patients (9%) had cardiovascular events, eight during the first 6 months without any differences between agents [Table 2].

**Table 2.** Side effects, tolerability, and dose adjustments according to PCSK9 mAbs agent

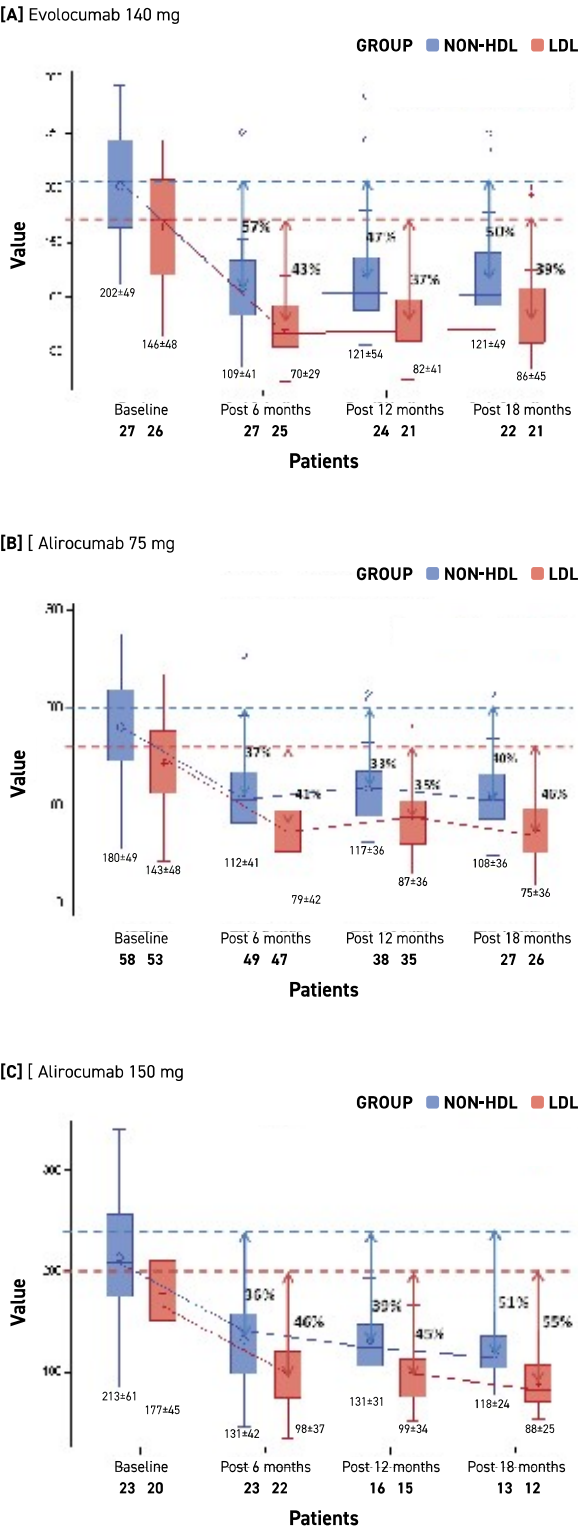
Variable	Cohort (n=115)	Evolocumab 140 mg (n=27)	Alirocumab 75 mg (n=65)	Alirocumab 150 mg (n=23)
<b>Side effects</b>				
None, n (%)	97 (84%)	26 (96%)	49 (75%)	22 (96%)
Myalgia, n (%)	6 (6%)	0 (0%)	5 (8%)	1 (4%)
Missing data, n (%)	12 (10%)	1 (4%)	11 (17%)	0 (0%)
Discontinuation of treatment, n (%)	7 (6%)	0 (0%)	5 (8%)	2 (9%)
Anti-PCSK9I changing to another type, n (%)	3 (3%)	0 (0%)	1 (2%)	2 (9%)
<b>Dose changing while on treatment</b>				
None, n (%)	74 (64%)	27 (100%)	27 (42%)	20 (87%)
Increasing dose, n (%)	25 (22%)	–	25 (38%)	–
Decreasing dose, n (%)	0 (0%)	–	–	0 (0%)
Missing data, n (%)	16 (14%)	–	13 (20%)	3 (13%)
<b>Cardiovascular events while on treatment</b>				
No events, n (%)	105 (91%)	24 (89%)	60 (92%)	21 (91%)
Events < 6 months, n (%)	8 (7%)	3 (11%)	3 (5%)	2 (9%)
Events > 6 months and < 1 year, n (%)	2 (2%)	0 (0%)	2 (3%)	0 (0%)

anti-PCSK9 = anti-protein convertase subtilisin/kexin type 9 (PCSK9), mAbs = monoclonal antibodies

**Figure 1.** Mean LDL-C and non-HDL-C levels along 18 months of follow-up non-HDL-C = non-high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol



**Figure 2.** LDL-C and non-HDL-C levels along follow-up according to the agents and doses non-HDL-C = non-high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol



## DISCUSSION

Our study results represent the real-life experience at a lipid clinic. The major indication for treatment with anti-PCSK9 mAbs treatment is statin intolerance, and most of the patients use it as a single agent. Two-thirds of the patients reached their LDL-C/non-HDL-C target levels. No clinically significant difference between the agents regarding their efficacy or tolerability was demonstrated.

Most of the initial data regarding the use of anti-PCSK9 mAbs were obtained from randomized controlled trials and performed in selective and well-defined very high-risk patient groups [2-5], whereas the real-life data, like ours, represent the actual every day clinical care.

The indication for anti-PCSK9 mAbs use in most of our patients was statin intolerance (n=97, 84%). This finding was in accordance with other similar reports [7-11], in contrast to the two leading CVO studies, FOURIER, and ODYSSEY OUTCOMES [4,5], where most of the patient were treated by high dose potent statins ± ezetimibe.

Consequently, most of our patients (n=102, 88%) as well as in other real-life reports (63% by Zafrir et al. [11], 70.2% by Bradley et al. [10]) were treated by anti-PCSK9 mAbs as a single lipid lowering agent. Sub-analysis of the ODYSSEY OUTCOMES study showed that alirocumab reduces the relative risk of major adverse cardiovascular events irrespective of background statin therapy, with high efficacy among the anti-PCSK9 mAbs single agent group [12].

The randomized controlled studies reported a 50–60% steady reduction in the LDL-C/non-HDL-C levels on anti-PCSK9 mAbs [2-5]. While other real-life reports found similar effect [7-9,13,14], our study results revealed rather lower efficacy (40–50%). This finding reflects the heterogeneity of the real-life patient population, as well as the wide range of LDL-C levels reduction, 0–90.3%, reported by Oren et al. [14].

Most of our patients reached their LDL-C/ non-HDL-C target levels (64% of the high risk and 70% of the very high-risk groups). Zafrir et al. [11] found that among those with established CVD, 55% achieved LDL-C level < 70 mg/dl.

These findings emphasize the low rates of concurrent lipid-lowering therapies in patients treated by anti-PCSK9 mAbs [10]. As the 2019 ESC/EAS guidelines recommend even lower target levels [13], it seems that treatment by only anti-PCSK9 mAbs might not be enough.

The entire experience discloses a high tolerability with the anti-PCSK9 mAbs. The main reported adverse event in our study was myalgia (6%), with similar rates for drug discontinuation. Similar findings were reported in other real-life studies, mainly injection site reactions, myalgias, and flu-like illness [7,9,14]. Zafrir et al. [7] reported higher side effects

and drug discontinuation rate (10% and 15%, respectively) in a similar Israeli cohort. In other studies, the rates of adverse events were 9%, 15.5%, and 12.5%, respectively [8,9,14], with discontinuation rates of 5% (28) and 2.5% [8].

The reported rate of cardiovascular events on anti-PCSK9 mAbs treatment in the real-life setting is limited due to relatively small study groups and short follow-up periods. Our findings demonstrated 9% event rate in the first year of the follow-up, most occurred at the first 6 months. Others had rates of 2.1% of coronary revascularization, 1.0% of hospitalization for unstable angina without any cardiovascular deaths [14].

We found no direct comparisons between the two anti-PCSK9 mAbs agents. Zafrir et al. [11] noted that attainment rates of LDL-C goals were higher in patients treated by evolucumab, although compared with alirocumab 150 mg dose the differences were rather small. Although evolucumab seemed to be more tolerated, our results did not support any clinically significant difference attributed to the efficacy or dosing method of the agents. This outcome should be clarified in further studies.

The strength of our study is that it represents the real-world data.

## LIMITATIONS

Limitations include the retrospective design, the relatively small study groups, and the short follow-up period with the subsequent lack of any comparison between agents and doses.

## CONCLUSIONS

In the real-world setting, anti-PCSK9 mAbs are used primarily as a single lipid lowering agent in high/very high cardiovascular risk population with statin intolerance. They are well tolerated and effective in LDL-C levels reduction. Further studies are warranted to clarify any comparison between agents and doses.

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## Capsule

### Sugar-microbiome-immune axis

Sugar in the context of a high-fat diet may act indirectly through effects on the microbiome and intestinal immune cells. **Kawano** et al. investigated the roles of type 3 innate lymphoid cells (ILC3s) and T helper 17 (TH17) cells, which produce interleukin-17. The authors found that ingested sugar selected for intestinal bacterial species that outcompete species of bacteria that would stimulate TH17 cell proliferation. The trouble is that TH17 cells also inhibit lipid uptake in mice on

a high-fat, high-sugar diet, so their depletion is metabolically problematic for the host. Removing sugar from high-fat diets prevents mice from becoming obese. The complex interplay between diet and immune responses to the gut microbiota is further complicated by the spectrum of microbial community compositions found among human beings.

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## Capsule

### Memory during wakefulness

The significance of sleep for long-term memory formation is well recognized. But what about the waking state? Does the wakeful mode of brain activity also promote memory consolidation? Using a novel object recognition task, **Sawangjit** and co-authors compared long-term memory formation in rats that had slept or remained awake during a critical 2-hour period after encoding the memory. Remote novel object recognition memory was assessed a week later. Unlike sleep-dependent consolidation,

wake consolidation strengthened a context-independent representation of objects and was independent of hippocampal function. Therefore, the brain's state of wakefulness is associated with a distinct mode of long-term memory formation that is partially associated with different memory traces.

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**The difference between false memories and true ones is the same as for jewels:  
it is always the false ones that look the most real, the most brilliant.**

Salvador Dalí (1904–1989), Spanish surrealist artist renowned for his technical skill, precise draftsmanship,  
and the striking and bizarre images in his work