in vivo *35*: 61-68 (2021)
doi:10.21873/invivo.12232

Review

PCSK9 Antibody-based Treatment Strategies for Patients With Statin Intolerance

ERRIKA VOUTYRITSA[1], CHRISTOS DAMASKOS[2], PARASKEVI FARMAKI[3], GEORGIOS KYRIAKOS[4], EVANGELOS DIAMANTIS[5], LOURDES VICTORIA QUILES-SÁNCHEZ[6], ANNA GARMPI[7], NIKOLAOS GARMPIS[2], ALEXANDROS PATSOURAS[8], ATHANASIA STELIANIDI[3] and SPYRIDON SAVVANIS[9]

[1]*NS Christeas Laboratory of Experimental Surgery and Surgical Research, Medical School, National and Kapodistrian University of Athens, Athens, Greece;*
[2]*Second Department of Propedeutic Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece;*
[3]*First Department of Pediatrics, Agia Sofia Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece;*
[4]*Sección de Endocrinología y Nutrición, Hospital General Universitario Santa Lucia, Cartagena, Spain;*
[5]*Department of Endocrinology and Diabetes Center, G. Gennimatas General Hospital, Athens, Greece;*
[6]*Centro de Salud Beniel, Murcia, Spain;*
[7]*Internal Medicine Department, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece;*
[8]*Second Department of Internal Medicine, Tzaneio General Hospital of Piraeus, Piraeus, Greece;*
[9]*Department of Internal Medicine, Elpis General Hospital of Athens, Athens, Greece*

Abstract. *Background: Statin intolerance refers to the inability of a patient to tolerate statin therapy, presenting muscle aches, pains, weakness and muscle inflammation. Thus, numerous patients are not treated with suitable statin-based therapy or take only very low doses. As a result, the desired decrease in low-density lipoprotein cholesterol (LDL-C) is not achieved, resulting in patients at a high risk for cardiovascular events, requiring an alternative lipid-lowering treatment. Common treatments manage to reduce the LDL-C level by up to 20%. Recently, new alternative treatment options have been proved to lower the LDL-C level by up to 70%. These treatment strategies are based on human monoclonal antibodies against protein convertase subtilisin/kexin 9 (PCSK9). Materials and Methods: Herein, we review the efficiency of anti-PCSK9 in treatment of hypercholesterolemic patients with statin intolerance. We focused on the use of PCSK9 inhibitors in statin-intolerant patients and we estimated the clinical results concerning the reduction of the mean LDL-C concentration and the side effects that were observed. Results: In the majority of cases, treatment strategy based on PCSK9 was successful and achieved the end-points. Conclusion: PCSK9 inhibition can be considered as a treatment of option for lipid-lowering in statin-intolerant patients.*

Correspondence to: Georgios Kyriakos, Sección de Endocrinología y Nutrición, Hospital General Universitario Santa Lucia, Cartagena, Spain. E-mail: giorgos6@yahoo.com

Key Words: Anti-PCSK9, statin intolerance, evolocumab, alirocumab, hypercholesterolemia.

Statin-based therapies are indicated for lowering low-density lipoprotein cholesterol (LDL-C) concentrations and are considered to be a safe option for the majority of patients with elevated LDL. However, a wide range of adverse effects have been attributed to this kind of treatment, indicating statin intolerance. Side effects derived from statin treatment in patients with statin intolerance are muscle symptoms, nausea, dyspepsia and headache and affect patients' quality of life (1, 2). Various risk factors have been reported, setting patients at a high risk of presenting statin-induced myopathy. The most common risk factors are advanced age, frailty, genetic factors and co-morbidities (3, 4). Moreover, an important factor that affects the risk of developing myopathy is the dosage used, an increased dose results in higher risk.

Concerning the current treatment options for statin-intolerant patients, when statin-based therapy results in adverse side-effects, a washout period is recommended. If

symptoms recede, a lower dose of the same statin is recommended. If the patient does not tolerate the given statin, an alternative statin should be considered. The most efficient and potent statins with a long half-life that can be recommended at low doses are atorvastatin, simvastatin, and rosuvastatin; Iess efficient drugs are fluvastatin and pravastatin (5, 6).

Additionally, non-statin therapies have been proven to lower the LDL-C level. For example, ezetimibe reduces LDL-C by 15-20%, by inactivating the Niemann-Pick C1-like 1 protein (NPC1L1) receptor, having few side-effects and being associated with reduced cardiovascular events in combination with a statin therapy (7-9). Other non-statin lipid-lowering therapies include bile acid sequestrants such as cholestyramine and colesevelam. Although these agents are poorly tolerated when they are given at increased doses, they are able to reduce the LDL-C level synergistically with statins (10).

The newest class of agents that are used in statin-intolerant patients are inhibitors of protein convertase subtilisin/kexin type 9 (PCSK9), which have been proven to significantly reduce the LDL-C level. The most commonly used drugs of this category are two monoclonal antibodies, evolocumab and alirocumab. Regarding the molecular pathway, when the LDL-C level in blood is increased, the monoclonal antibody attaches to PCSK9 and as a result, inhibits the interaction between it and the LDL receptor. PCSK9 inhibition results in increased expression of LDL receptors and therefore the LDL-C concentration is reduced. Importantly, these drugs have also been reported to reduce the rate of cardiovascular events (11-16).

The aim of this review was to investigate the utilization of PCSK9 inhibitors in statin-intolerant patients with muscle-related side-effects. The safety and the effectiveness of these agents was assessed.

Materials and Methods

This review article was based on a systematic search conducted in MEDLINE (*via* PubMed) library in order to retrieve articles focusing on use of PCSK9 inhibitors in statin-intolerant patients. The search strategy was based on the use of key words such as anti-PCSK9 antibodies, statin intolerance, evolocumab, alirocumab and hypercholesterolemia. A total of 61 records were identified. Some of them were only abstracts, whereas others were not completely relevant to the topic. These articles were excluded. Following removal of the duplicates, 10 records remained. The full-text articles assessed for eligibility were 10 and none of them was excluded. The inclusion process is presented in Figure 1.

Results

In 2012, Giugliano *et al*. conducted a trial in which the efficiency and the safety of evolocumab, a human monoclonal IgG2 antibody, as a PCSK9 inhibitor were assessed in statin-intolerant hypercholesterolemic patients (Table I) (17). During this study, 631 patients aged 18-80 years on a stable statin dose with hypercholesterolemia were randomly treated with subcutaneous injections of different doses of evolocumab or placebo every 2 weeks or 4 weeks. After 12 weeks, not only was the mean LDL-C level reduced but also no dose-related or dose-frequency-related increase in side-effects were reported. In contrast, in another study, although the LDL-C concentration was reduced, four serious complications were reported during the evolocumab treatment: Coronary artery disease, acute pancreatitis, hip fracture, and syncope, while myalgia was the main treatment-related side-effect during the study, occurring in 15.6% of the patients (Table I) (18).

Another antibody to PCSK9, alirocumab, has also been investigated. Moriarty *et al*., presented a study in which alirocumab was compared to ezetimibe in patients at cardiovascular risk with statin intolerance due to muscle side-effects (Table I) (19). During this study, 361 patients were treated with subcutaneous and oral placebo for 4 weeks. Patients in whom muscle-related symptoms were observed were excluded. The rest of the patients were randomized to alirocumab, alirocumab plus placebo, ezetimibe, ezetimibe plus placebo, atorvastatin or atorvastatin plus placebo for 24 weeks. According to the clinical findings, alirocumab resulted in greater LDL-C reductions compared to ezetimibe in statin-intolerant patients, while fewer skeletal-muscle side-effects were observed compared to atorvastatin. In line with these findings, the ODYSSEY DM-DYSLIPIDEMIA randomized trial investigated the safety and efficiency of alirocumab in individuals with type 2 diabetes mellitus and mixed dyslipidemia taking the maximally tolerated dose of statin (Table I) (20). A total of 413 individuals were randomized to receive 75-150 mg alirocumab every 2 weeks or lipid-lowering common treatment including no additional lipid-lowering therapy, fenofibrate, ezetimibe, omega-3 fatty acid, and nicotinic acid. Alirocumab proved to be more efficient in reducing the mean non-HDL-C, LDL-C (−43.0%), apolipoprotein B (−32.3%), and total cholesterol (−24.6%). In addition, it was generally well-tolerated and the incidence of treatment-related adverse events were similar to other study cohorts.

In addition, Teramoto *et al*. investigated the efficiency of alirocumab in lowering LDL-C (Table I) (21). In this study, 163 patients with hypercholesterolemia were randomized to a placebo-controlled study. During the 12-week therapy period, patients will be randomized equally to receive alirocumab subcutaneously (150 mg/4 weeks), placebo (150 mg/4 weeks), alirocumab (150 mg/2 weeks), or placebo (150 mg/2 weeks). The clinical results, the safety and tolerability of alirocumab will be reported in the future.

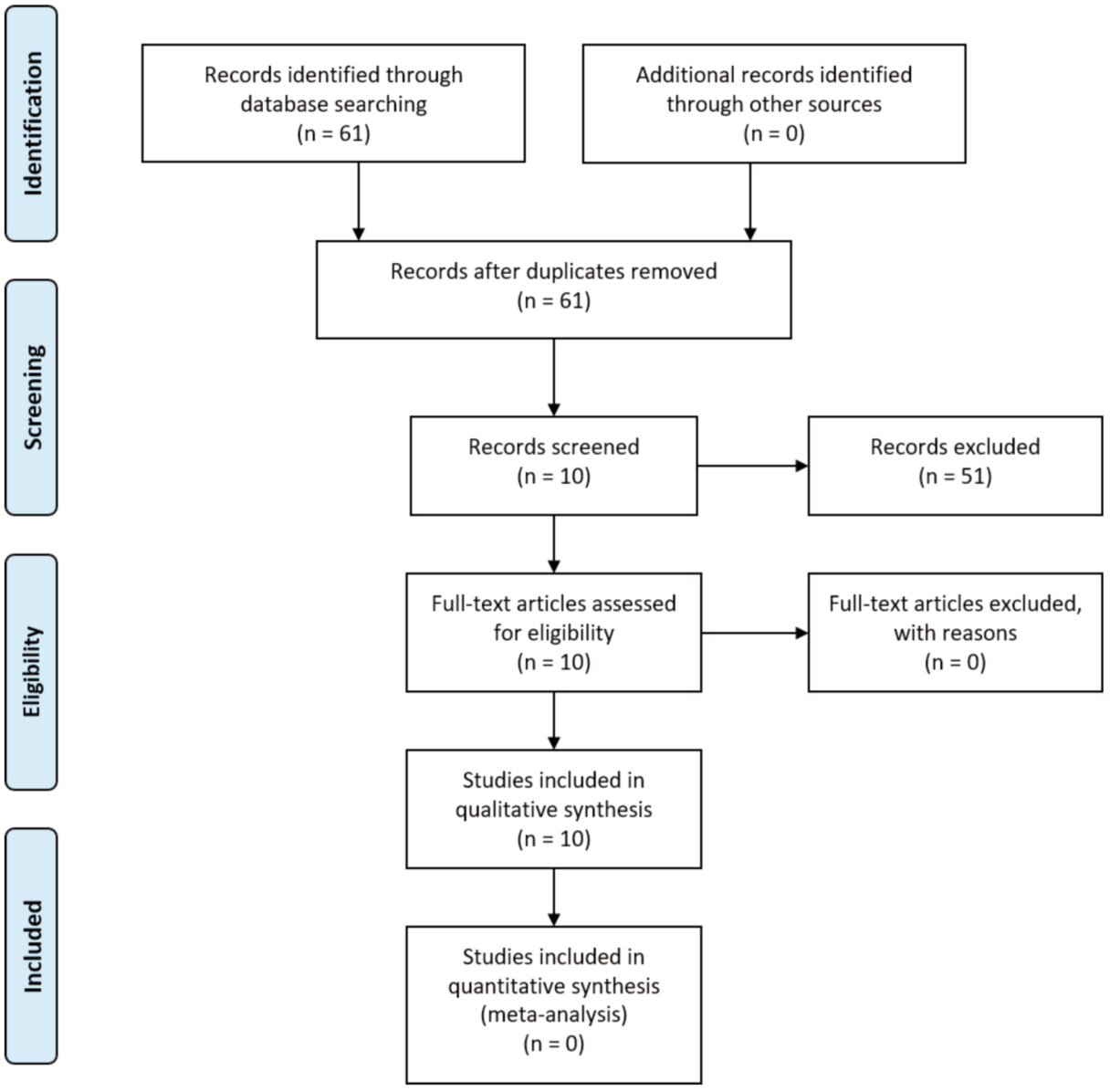

Figure 1. *PRISMA flow diagram for the current literature review.*

Cho *et al*. conducted a trial in which evolocumab was compared to ezetimibe in hypercholesterolemic patients with statin-associated muscle symptoms (Table I) (22). During this study, 307 patients with elevated LDL-C were tested in a 12-week study. Patients were randomized to evolocumab plus ezetimibe (2: 1). The mean LDL-C level was 4.99 mmol/l. Several statin-related complications were observed: Myalgia in 80% of patients, weakness in 39%, and more serious complications in 20%. Moreover, another study group investigated the safety and efficiency of evolocumab up to 2 years in patients with statin intolerance (Table I) (23). During this study, 382 statin-intolerant patients were tested and re-randomized to evolocumab at a dose of 140 mg weekly or 420 mg monthly (2: 1) or to a standard therapy. After year 1, 98% of the patients had been treated with evolocumab plus a standard therapy. The mean LDL-C concentration was 4.97-5.02 mmol/l (range=192-194 mg/dl). A reduction of 13% was observed in patients treated with the standard therapy and 57% in patients treated with evolocumab plus standard therapy in the first year, and 59% in patients treated with evolocumab plus standard therapy in the second year. Regarding adverse effects, muscle-related events were observed in 16% of patients treated with the standard therapy, and in 14% of those treated with

Table I. *Clinical trials conducted in the current literature review.*

Author (Ref)	PCSK9 inhibitor	Patients	Indication	Drug doses	Study duration	Results	Procedural complications
Giugliano *et al*. 2012 (17)	Evolocumab	631, With hypercholesterolemia; 311 male, age 18-80 years	LDL-C >2.2 mmol/l on a stable dose of statin.	Randomly treated with 70 mg (n=79), 105 mg (n=79), or 140 mg (n=78) evolocumab, or placebo (n=78) every 2 weeks, or 280 mg (n=79), 350 mg (n=79) and 420 mg (n=80) evolocumab and placebo (n=79) every 4 weeks.	12 weeks	Mean LDL-C decreased (41.8-66.1%; p<0.0001 for each dose *vs*. placebo).	No treatment-related serious adverse events.
Sullivan *et al*. 2012 (18)	Evolocumab	160, Statin-intolerant; 58 male, mean age 62 years	Muscle-related side-effects.	Randomized equally to: Evolocumab alone at doses of 280 mg, 350 mg, or 420 mg; 420 mg evolocumab+10 mg of ezetimibe; or 10 mg of ezetimibe+placebo.	12 weeks	LDL-C levels were 280 mg evolocumab: reduction of 67 mg/dl 350 mg evolocumab: reduction of 70 mg/dl 420 mg evolocumab: reduction of 91 mg/dl 420 mg evolocumab/ ezetimibe: reduction of 110 mg/dl placebo/ ezetimibe: reduction of 14 mg/dl 420 mg	Myalgia
Moriarty *et al*. 2015 (19)	Alirocumab	361, With statin intolerance; 172 male, mean age 63 years	Unable to tolerate ≥2 statins, even at lowest dose, due to muscle symptoms.	Patients were randomized double-blind (2: 2: 1) to 75 mg alirocumab s.c. q2w+oral placebo, 10 mg/d ezetimibe (+placebo s.c. q2w), or 20 mg/d atorvastatin (rechallenge; +placebo s.c. q2w for 24 weeks).	24 weeks	Mean LDL-C reduced by 45.0% (2.2%) with alirocumab *vs*. 14.6% (2.2%) with ezetimibe.	Skeletal muscle-related events were less frequent with alirocumab *vs*. atorvastatin.
Cho *et al*. 2016 (20)	Evolocumab	307; 166 Male, mean age 62 years	Elevated LDL-C, statin-associated muscle symptoms	Patients were randomized to 140 mg evolocumab q2w+daily oral placebo; s.c. 420 mg evolocumab monthly plus daily oral placebo; SC placebo q2w plus daily oral ezetimibe 10 mg; and s.c. placebo monthly+daily oral 10 mg ezetimibe.	12 weeks	Mean±SD LDL-C 4.99±1.51 mmol/l.	Myalgia in 80% of patients, weakness in 39%, more serious complications in 20%.
Nissen *et al*. 2016 (21)	Evolocumab	511; Sex NR, age 18-80 years	Unable to tolerate an effective dose of a statin	420 mg Evolocumab monthly and with 10 mg ezetimibe daily.	24 weeks	LDL-C <70 mg/dl.	Creatine kinase elevation accompanied by muscle symptoms
Müller-Wieland *et al*. 2017 (22)	Alirocumab *vs*. usual care (US, no therapy; fenofibrate; ezetimibe; omega-3 fatty acid; nicotinic acid)	413; 215 Male, age 18-80 years	Non-HDL-C ≥100 mg/dl (≥2.59 mmol/l), and triglycerides ≥150 and <500 mg/dl (≥1.70 and <5.65 mmol/l).	75 mg Alirocumab q2w increased to 150 mg q2w at week 12 if week 8 non-HDL-C ≥2.59 mmol/l (100 mg/dl) or UC for 24 weeks.	24 weeks	No change in HDL-C level was observed from baseline to week 24 in patients treated with alirocumab *vs*. usual care.	Treatment-emergent adverse events in 68.4% (alirocumab) and 66.4% (UC).

Table I. *Continued*

Table I. *Continued*

Author (Ref)	PCSK9 inhibitor	Patients	Indication	Drug doses	Study duration	Results	Procedural complications
Sbrana *et al*. 2017 (23)	Evolocumb and alirocumab	18; 13 Male, mean age 62 years	Lp(a)-hyperlipo-proteinemia (>60 mg/dl)	Injectable PCSK9 monoclonal antibodies q2w on top of patient therapy for 12±4 weeks (evolocumab in 15; alirocumab in 3).	3 months	Reductions: Total cholesterol: −35%, LDL-C: −51%, Lp(a) −20%; LDL-C <70 mg/dl in 5/18, 71-100 mg/dl in 7/18, >100 mg/dl in 6/18	Complications in 2/18 patients on evolocumab (flu-like syndrome; episodes of mild difficulty maintaining concentration).
Teramoto *et al*. 2018 (24)	Alirocumab	163, Sex NR, age above 20 years	LDL-C ≥100 mg/dl	Randomized equally to: Alirocumab s.c. (150 mg q4w), placebo (150 mg q4w), alirocumab (150 mg q2w), or placebo (150 mg q2w).	12 weeks	Awaited	NR
Cho *et al*. 2018 (25)	Evolocumab	382, Statin-intolerant; sex NR, mean age 61 years	Statin intolerance	Randomized 2: 1 to: Evolocumab (140 mg q2w or 420 mg q4w+SOC or SOC during year 1, and thereafter, evolocumab plus SOC.	12 weeks	Median reduction from baseline LDL-C: 13% for SOC and 57% for evolocumab+SOC at year 1, and 59% for evolocumab+SOC at year 2.	Muscle-related adverse events
Shapiro *et al*. 2019 (26)	Evolocumab	895; 457 Male, median age 59 years	Hyperchole-sterolemia or statin intolerance	Evolocumab at 140 mg q2w or 420 mg q4w.	12 weeks	Baseline mean LDL-C=133.6 mg/dl, median Lp(a)= 46.4 mg/dl	Discordant response in 165 patients.

PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL: Low-density lipoprotein; q2w: once every two weeks; sc: subcutaneous; SD: standard deviation; NR: not reported; HDL: High-density lipoprotein; UC: usual care; Lp(a): Lipoprotein(a); q4w: once every four weeks.

evolocumab plus the standard therapy at year 1, and in 11% of the patients treated with evolocumab plus the standard therapy at year 2. According to the clinical findings, evolocumab plus the standard therapy was shown to be safe, tolerable, and efficient for up to 2 years in statin-intolerant patients.

In the same year, Nissen *et al*., reported on the efficiency of evolocumab compared to ezetimibe in hypercholesterolemic patients during a 24-week trial (Table I) (24). Patients treated with 420 mg evolocumab monthly compared to 10 mg ezetimibe daily managed to attain LDL-C <70 mg/dl. As a result, evolocumab gave promising results compared with ezetimibe in statin-intolerant patients and allowed researchers to better understand the potential role of PCSK9 inhibitors in the treatment of these challenging patients.

Sbrana *et al*. enrolled 18 individuals, with a mean age of 62 years, with hypercholesterolemia, cardiovascular disease, and statin intolerance (Table I) (25). The efficiency of PCSK9 inhibitors was investigated. Evolocumab was administered to 15 patients, and alirocumab to three. After 3 months of therapy, a decrease in total cholesterol, LDL-C and Lp(a) levels was achieved. Importantly, in five patients, the level of LDL-C was reduced to <70 mg/dl, seven presented LDL-C levels between 71 and 100 mg/dl, and six continued to have LDL-C levels above 100 mg/dl. Adverse side-effects occurred in two patients treated with evolocumab. According to the results, PCSK9 inhibitors were found to be novel therapeutic tools for statin-intolerant patients with hypercholesterolemia. However, deeper investigation is needed.

Finally, Shapiro *et al*., conducted a trial, in which LDL-C and Lp(a) lowering by evolocumab was investigated (Table I) (26). In this study, 895 patients with hypercholesterolemia, or statin intolerance participated in a 12-week study. Baseline mean level of LDL-C was 133.6 mg/dl and the median Lp(a) level was 46.4 mg/dl. A discordant response was detected in 165 patients. Moreover, the prevalence of discordance increased when considering those with baseline Lp(a) concentrations >30 mg/dl (26.5%) or >50 mg/dl (28.6%). On the basis of these data, high prevalence of discordance in LDL-C and Lp(a) reduction in the case of

evolocumab was demonstrated. As a result, evolocumab provides promising results that need further investigation.

Discussion

Statin intolerance is a common problem among patients treated with statins (27). These patients, being unable to tolerate statin therapy, present muscle-related complications. Therefore, various alternatives treatment options have been reported in order to reduce the LDL-C concentration (28-32). PCSK9 inhibitors have been shown to resulted in a decrease of LDL-C level by up to 70% and have been approved for patients with primary hypercholesterolemia, for patients with statin intolerance and for patients with atherosclerotic cardiovascular disease requiring LDL-C lowering (33, 34).

According to a published review, PCSK9 inhibitors have been a preferred treatment for patients with statin intolerance (35, 36). In particular, two monoclonal antibodies, evolocumab and alirocumab, are considered as treatment of choice, resulting in LDL-C reduction >50%. Arilocumab is associated with a low rate of muscle complications, while evolocumab is related to significantly great reduction of LDL-C concentrations without presenting muscle-related adverse events.

In a recent review, it was suggested that in patients with statin intolerance, presenting muscle pain, treatment with another statin should be recommended (37). The most effective and tolerable statins that patients can be treated with are atorvastatin and rosuvastatin. Moreover, an alternative agent for patients who are not able to tolerate any of the statins is ezetimibe. However, this review also suggests that if LDL cholesterol targets are not achieved, PCSK9 inhibitors may be a valuable option. In patients at high risk of cardiovascular events, these inhibitors can be considered as a suitable treatment tool, resulting in good results.

On the other hand, there have been reports arguing against treatment with PCSK9 inhibitors, such as evolocumab, in statin-intolerant patients (38). In these studies, it was indicated that although preliminary clinical findings were promising, long-term outcomes were controversial, as PCSK9 inhibitors have not yet been proved to reduce cardiovascular events. Moreover, it was suggested that PCSK9 inhibitors are themselves associated with muscle-related adverse effects. Additionally, PCSK9 inhibitor-based therapies are costly and, as a result, are an inappropriate treatment option. According to their findings cardiovascular and noncardiovascular mortality was reduced in patients receiving statin-based therapy, while PCSK9 inhibitors need further investigation as LDL-C lowering therapy.

Recently a review suggested that the better choice for statin-intolerant patients is the re-initiation of therapy with an alternative statin which is related to better persistence (39). Higher tolerance is linked to atorvastatin and rosuvastatin. Restarting therapy based on a different statin may allow clinicians to achieve better therapy selection. Given that statin-taking behaviors may differ, this review recommended that restarting therapy with a different statin can lead to better outcomes. However, innovative strategies need to be undertaken to improve statin compliance.

Studies that will primarily test the effects of monoclonal antibodies to PCSK9 on long-term cardiovascular results should be conducted in order to determine whether the documented LDL-C reduction and various other promising impacts on short-term clinical findings lead to long-term cardiovascular benefit (40). The promising and meaningful evidence of the clinical benefits provided of these agents should lead to cost-effectiveness analyses. Whether this treatment option is effective for cardiovascular risk reduction remains to be determined. The expected novel insights from ongoing trials will notably influence future suggestions of these promising therapies for challenging statin-intolerant patients.

Conclusion

In conclusion, numerous studies have been published about the usefulness of PCSK9 inhibition as a treatment option for lipid-lowering in statin-intolerant patients. However, further clinical trials should be conducted and deeper investigation is needed concerning the safety and the efficiency of this treatment option.

Conflicts of Interest

The Authors report no conflicts of interest in this work.

Authors' Contributions

Savvanis S. and Diamantis E. designed the study. Voutyritsa E., Farmaki P. and Patsouras A. wrote the article. Voutyritsa E., Farmaki P., Diamantis E., Quiles-Sánchez LV. and Kyriakos G. collected the data. Quiles-Sánchez LV., Kyriakos G. Stelianidi A. offered scientific advice. Diamantis E., Damaskos C., Garmpi A., Garmpis N. revised the article. Savvanis S. was the supervisor.

References

1 Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK and Ford I: Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. Lancet *375*: 735-742, 2010. PMID: 20167359. DOI: 10.1016/S0140-6736(09)61965-6

2 Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D and Ebrahim S: Unintended effects of statins from observational studies in the general population: systematic review and meta-

analysis. BMC Med *12*: 51, 2014. PMID: 24655568. DOI: 10.1186/1741-7015-12-51

3 Chatzizisis YS, Koskinas KC, Misirli G, Vaklavas C, Hatzitolios A and Giannoglou GD: Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Saf *33*: 171-187, 2010. PMID: 20158283. DOI: 10.2165/11319380-000000000-00000

4 Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN and European Atherosclerosis Society Consensus Panel: Statin-associated muscle symptoms: impact on statin therapy. European Atherosclerosis Society consensus panel statement on assessment, etiology and management. Eur Heart J *36*: 1012-1022, 2015. PMID: 25694464. DOI: 10.1093/eurheartj/ehv043

5 Bruckert E, Hayem G, Dejager S, Yau C and Begaud B: Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther *19*: 403-414, 2005. PMID: 16453090. DOI: 10.1007/s10557-005-5686-z

6 Jones P, Kafonek S, Laurora I and Hunninghake D: Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Am J Cardiol *81*: 582-587, 1998. PMID: 9514454. DOI: 10.1016/s0002-9149(97)00965-x

7 Norata GD, Ballantyne CM and Catapano AL: New therapeutic principles in dyslipidaemia: focus on LDL and Lp(a) lowering drugs. Eur Heart J *34*: 1783-1789, 2013. PMID: 23509227. DOI: 10.1093/eurheartj/eht088

8 Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM and IMPROVE-IT Investigators: Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med *372*: 2387-2397, 2015. PMID: 26039521. DOI: 10.1056/NEJMoa1410489

9 Catapano AL and Ference BA: IMPROVE-IT and genetics reaffirm the causal role of LDL in cardiovascular disease. Atherosclerosis *241*: 498-501, 2015. PMID: 26091974. DOI: 10.1016/j.atherosclerosis.2015.06.008

10 Rifkind BM: Lipid research clinics coronary primary prevention trial: Results and implications. Am J Cardiol *54*: 30C-34C, 1984. PMID: 6382999. DOI: 10.1016/0002-9149(84)90854-3

11 Bergeron N, Phan BA, Ding Y, Fong A and Krauss RM: Proprotein convertase subtilisin/kexin type 9 inhibition: A new therapeutic mechanism for reducing cardiovascular disease risk. Circulation *132*: 1648-1666, 2015. PMID: 26503748. DOI: 10.1161/CIRCULATIONAHA.115.016080

12 Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG and Boileau C: Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. Nat Genet *34*: 154-156, 2003. PMID: 12730697. DOI: 10.1038/ng1161

13 Gouni-Berthold I: PCSK9 antibodies: A new class of lipid-lowering drugs. Atheroscler Suppl *18*: 21-27, 2015. PMID: 25936300. DOI: 10.1016/j.atherosclerosissup.2015.02.003

14 Gouni-Berthold I, Descamps OS, Fraass U, Hartfield E, Allcott K, Dent R and März W: Systematic review of published phase 3 data on anti-PCSK9 monoclonal antibodies in patients with hypercholesterolaemia. Br J Clin Pharmacol *82*: 1412-1443, 2016. PMID: 27478094. DOI: 10.1111/bcp.13066

15 Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA and Opst LDL Cholesterol (OSLER) Investigators: Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med *372*: 1500-1509, 2015. PMID: 25773607. DOI: 10.1056/NEJMoa1500858

16 Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ and ODYSSEY Long-term Investigators: Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med *372*: 1489-1499, 2015. PMID: 25773378. DOI: 10.1056/NEJMoa1501031

17 Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS and LAPLACE-TIMI 57 Investigators: Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): A randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet *380*: 2007-2017, 2007. PMID: 23141813. DOI: 10.1016/S0140-6736(12)61770-X

18 Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, Wasserman SM and Stein EA: Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial. JAMA *308*: 2497-2506, 2012. PMID: 23128163. DOI: 10.1001/jama.2012.25790

19 Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA and ODYSSEY ALTERNATIVE Investigators: Efficacy and safety of alirocumab *vs*. ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. J Clin Lipidol *9*: 758-769, 2015. PMID: 26687696. DOI: 10.1016/j.jacl.2015.08.006

20 Müller-Wieland D, Leiter LA, Cariou B, Letierce A, Colhoun HM, Del Prato S, Henry RR, Tinahones FJ, Aurand L, Maroni J, Ray KK and Bujas-Bobanovic M: Alirocumab *vs*. usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: The ODYSSEY DM-DYSLIPIDEMIA randomized trial. Diabetes Obes Metab *20*: 1479-1489, 2018. PMID: 29436756. DOI: 10.1111/dom.13257

21 Teramoto T, Kondo A, Kiyosue A, Harada-Shiba M, Ishigaki Y, Tobita K, Kawabata Y, Ozaki A, Baccara-Dinet MT and Sata M: Efficacy and safety of alirocumab in patients with hypercholesterolemia not adequately controlled with non-statin lipid-lowering therapy or the lowest strength of statin: ODYSSEY NIPPON study design and rationale. Lipids Health Dis *16*: 121, 2017. PMID: 28623954. DOI: 10.1186/s12944-017-0513-7

22 Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, Xue A, Scott R, Wasserman SM and Stroes E: Clinical profile of statin intolerance in the phase 3 GAUSS-2 Study. Cardiovasc Drugs Ther *30*: 297-304, 2016. PMID: 26936841. DOI: 10.1007/s10557-016-6655-4

23 Cho L, Dent R, Stroes ESG, Stein EA, Sullivan D, Ruzza A, Flower A, Somaratne R and Rosenson RS: Persistent safety and efficacy of evolocumab in patients with statin intolerance: A subset analysis of the OSLER open-label extension studies. Cardiovasc Drugs Ther *32*: 365-372, 2018. PMID: 30073585. DOI: 10.1007/s10557-018-6817-7

24 Nissen SE, Dent-Acosta RE, Rosenson RS, Stroes E, Sattar N, Preiss D, Mancini GB, Ballantyne CM, Catapano A, Gouni-Berthold I, Stein EA, Xue A, Wasserman SM, Scott R, Thompson PD and GAUSS-3 Investigators: Comparison of PCSK9 inhibitor evolocumab *vs*. ezetimibe in statin-intolerant patients: Design of the goal achievement after utilizing an anti-PCSK9 antibody in statin-intolerant subjects 3 (GAUSS-3) Trial. Clin Cardiol *39*: 137-144, 2016. PMID: 26946077. DOI: 10.1002/clc.22518

25 Sbrana F, Dal Pino B, Bigazzi F, Ripoli A, Passino C, Gabutti A, Pasanisi EM, Petersen C, Valleggi A, Todiere G, Barison A, Giannoni A, Panchetti L, Becherini F, Pianelli M, Luciani R and Sampietro T: Statin intolerance in heterozygous familial hypercolesterolemia with cardiovascular disease: After PCSK-9 antibodies what else? Eur J Prev Cardiol *24*: 1528-1531, 2017. PMID: 28555526. DOI: 10.1177/2047487317712419

26 Shapiro MD, Minnier J, Tavori H, Kassahun H, Flower A, Somaratne R and Fazio S: Relationship between low-density lipoprotein cholesterol and lipoprotein(a) Lowering in response to PCSK9 inhibition with evolocumab. J Am Heart Assoc *8*: e010932, 2019. PMID: 30755061. DOI: 10.1161/JAHA.118.010932

27 Snejdrlova M, Altschmiedova T, Vrablik M, Stulc T, Lastuvka J, Lanska V and Ceska R: Statin intolerance in clinical practice. Curr Atheroscler Rep *22*: 27, 2020. PMID: 32495058. DOI: 10.1007/s11883-020-00845-9

28 Roh JW, Chun KH, Kang M, Lee CJ, Oh J, Shim CY, Ahn CM, Kim JS, Kim BK, Park S, Chang HJ, Hong GR, Ko YG, Kang SM, Choi D, Ha JW, Hong MK, Jang Y and Lee SH: PRavastatin *versus* FlUVastatin After Statin Intolerance: The PRUV-intolerance study with propensity score matching. Am J Med *132*: 1320-1326.e1, 2019. PMID: 31278931. DOI: 10.1016/j.amjmed.2019.06.003

29 Soran H, France M, Adam S, Iqbal Z, Ho JH and Durrington PN: Quantitative evaluation of statin effectiveness *versus* intolerance and strategies for management of intolerance. Atherosclerosis *306*: 33-40, 2020. PMID: 32683135. DOI: 10.1016/j.atherosclerosis.2020.06.023

30 Marazzi G, Campolongo G, Pelliccia F, Calabrò Md P, Cacciotti L, Vitale C, Massaro R, Volterrani M and Rosano G: Usefulness of low-dose statin plus ezetimibe and/or nutraceuticals in patients with coronary artery disease intolerant to high-dose statin treatment. Am J Cardiol *123*: 233-238, 2019. PMID: 30420184. DOI: 10.1016/j.amjcard.2018.09.041

31 Scolaro B, Nogueira MS, Paiva A, Bertolami A, Barroso LP, Vaisar T, Heffron SP, Fisher EA and Castro IA: Statin dose reduction with complementary diet therapy: A pilot study of personalized medicine. Mol Metab *11*: 137-144, 2018. PMID: 29503145. DOI: 10.1016/j.molmet.2018.02.005

32 Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, Kelly S and Stroes ESG: Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc *8*: e011662, 2019. PMID: 30922146. DOI: 10.1161/JAHA.118.011662

33 Cannon CP, Sanchez RJ, Klimchak AC, Khan I, Sasiela WJ, Reynolds MR and Rosenson RS: Simulation of the impact of statin intolerance on the need for ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitor for meeting low-density lipoprotein cholesterol goals in a population with atherosclerotic cardiovascular disease. Am J Cardiol *23*: 1202-1207, 2019. PMID: 30736965. DOI: 10.1016/j.amjcard.2019.01.028

34 Schreml J and Gouni-Berthold I: Role of anti-PCSK9 antibodies in the treatment of patients with statin intolerance. Curr Med Chem *25*: 1538-1548, 2018. PMID: 28618994. DOI: 10.2174/0929867324666170616111647

35 Davidson ER, Snider MJ, Bartsch K, Hirsch A, Li J and Larry J: Tolerance of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients with self-reported statin intolerance. J Pharm Pract *33*: 276-282, 2020. PMID: 30222031. DOI: 10.1177/0897190018799218

36 Alonso R, Cuevas A and Cafferata A: Diagnosis and management of statin intolerance. J Atheroscler Thromb *26*: 207-215, 2019. PMID: 30662020. DOI: 10.5551/jat.RV17030

37 Fischer S and Julius U: Management of patients with statin intolerance. Atheroscler Suppl *30*: 33-37, 2017. PMID: 29096858. DOI: 10.1016/j.atherosclerosissup.2017.05.013

38 Waters DD, Hsue PY and Bangalore S: PCSK9 inhibitors for statin intolerance? JAMA *315*: 1571-1572, 2016. PMID: 27039138. DOI: 10.1001/jama.2016.3670

39 Ofori-Asenso R, Ilomaki J, Tacey M, Zomer E, Curtis AJ, Si S, Zullo AR, Korhonen MJ, Bell JS, Zoungas S and Liew D: Switching, discontinuation, and reinitiation of statins among older adults. J Am Coll Cardiol *72*: 2675-2677, 2018. PMID: 30466527. DOI: 10.1016/j.jacc.2018.08.2191

40 Koskinas K, Wilhelm M and Windecker S: Current treatment of dyslipidaemia: PCSK9 inhibitors and statin intolerance. Swiss Med Wkly *146*: w14333, 2016. PMID: 27400448. DOI: 10.4414/smw.2016.14333

Received August 1, 2020
Revised August 31, 2020
Accepted September 7, 2020