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Review

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Statin Intolerance: an Overview of the Current Status and Possible Treatment Options

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ABSTRACT

Lowering serum low-density lipoprotein cholesterol (LDL-C) is the mainstay for reduction of risk of cardiovascular disease (CVD), the second most common cause of death in Korea. The 2015 Korean guidelines for management of dyslipidemia strongly recommend the use of statins in patients at risk of CVD. Statin therapy, which is the gold standard for CVD, reduces LDL-C level by 40% to 60% and is generally well tolerated. However, many patients are intolerant to statins and discontinue therapy or become nonadherent to therapy because of actual/perceived side effects. The most common of these side effects is the statin-associated muscle symptom (SAMS). Discontinuation and repetitive re-challenge with statins can help identify SAMS. If serum creatinine kinase level is more than 10 times the upper limit of normal, statin therapy must be stopped immediately, and the physician should identify possible causes including rhabdomyolysis and treat appropriately. In other patients, it might help to switch to a less potent statin or to use statins at intermittent non-daily dosing. To achieve target LDL-C level, non-statin lipid-lowering therapies such as dietary modifications, ezetimibe, and bile acid sequestrants may be added. Several new drugs have recently been approved for lowering LDL-C level. Alirocumab and evolocumab are monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9, and both drugs cause large reductions in LDL-C, similar to statins. Lomitapide and mipomersen are orphan drugs used as adjuncts to other lipid-lowering therapies in patients with homozygous familial hypercholesterolemia.

Keywords: Statins; Lipids; Cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) accounts for nearly 17 million deaths in the world every year and is the second most common cause of death in Korea.[1,2] Coronary artery disease (CAD) is the most prevalent type of CVD in Korea; in 2016, the mortality rate due to CAD was 58.2 deaths per 100,000.[2] In the same year, 45.8 per 100,000 died due to cerebrovascular diseases.[2] The prevalence of dyslipidemia, the main regulating risk factor for CVD, among the

Korean population varies from 30% to over 60% with a reported increase in total and low-density lipoprotein cholesterol (LDL-C) levels.[1]

Statins are the drugs of choice for treating dyslipidemia. These are usually safe, well-tolerated and effective cholesterol-lowering drugs irrespective of the patients' age, gender, high/low cardiovascular (CV) risk, and more/less intensive therapy.[3,4] However, their side effects such as skeletal muscle toxicity,[5] hepatotoxicity[6] and decrease in vascular smooth muscle contractility,[7] cannot be overlooked because of the increased incidence of dyslipidemia and increased consumption volume of statins countrywide.[7] Some people are intolerant to statins and side effects are often more severe in such people; this often leads to nonadherence to statin therapy. Therefore, in statin-intolerant patients, there is a need for effective alternative therapies. However, we do not have representative data of the prevalence of statin intolerance or the rate of drug discontinuation due to specific side effects of statins in Korea.

STATIN THERAPY IN DYSLIPIDEMIA

Birth of statins

The rate of cholesterol synthesis in the liver is controlled by 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Akira Endo, a Japanese scientist, isolated citrinin (1971) and compactin (1973) from culture broths of fungi.[7] The compounds showed strong HMG-CoA reductase inhibition.[7] In 1978, compactin was first used in a patient at a daily dose of 500 mg and showed excellent results with the serum cholesterol dropping from 1,000 mg/dL to about 700 mg/dL.[7] Three years later, compactin was reported to decrease plasma LDL-C level by 29% in patients with heterozygous familial hypercholesterolemia (FH).[8] This led to the search for similar compounds. Lovastatin, with a chemical structure very similar to compactin, became the first commercial statin in 1987. It was followed by semisynthetic statins such as simvastatin and pravastatin and synthetic statins such as fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. Atorvastatin and rosuvastatin are the most commonly used statins today.

Benefits of statin usage

Statins have become the first-line therapy for reducing the risk of CVD mortality and morbidity as well as for reducing the need for coronary artery revascularization procedures in people who have suboptimal lipid profile, with or without other risk factors.[9] Statins are lifesaving as they help primary prevention of CAD by rapidly lowering the LDL-C. Intensive therapy with moderate and high intensity statin can lower LDL-C by 50% or more.[10] Even low-intensity statin therapy has been shown to reduce LDL-C levels by about 30%.[10] Improvement in lipid profile is known to reduce the risk of CVD.[11] Statins have been reported to reduce the incidence of fatal and nonfatal strokes by 31% and 37%, respectively.[9] They also have efficacy to lower triglyceride (TG) and very low density lipoproteins (VLDL) levels. In addition, statins reduce platelet aggregation, thrombus formation, inflammation, and C-reactive protein levels, showing pleiotropic effects.[1,9,12]

Global clinical practice guidelines as well as Korean guidelines from Korean Society for Lipid and Atherosclerosis strongly recommend the use of statins in patients at risk of CVD.[1,12]

Statin-related adverse events and statin intolerance

Approximately 10% to 15% of patients are unable to tolerate statins in the doses required to sufficiently reduce the risk of CVD.[13,14] The commonest signs and symptoms of statin

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Table 1. Potential adverse effects of statins[5,9,12,13,21]

Level of evidence	Adverse effect
Adverse effects with good supportive evidence	Myopathy (myalgia, myositis, rhabdomyolysis)
	Increase in liver function enzymes
	New onset diabetes mellitus
Adverse effects with little or no supportive evidence	Cancer
	Intracerebral hemorrhage (stroke)
	Cognitive decline
	Lung disease
	Erectile dysfunction
	Fatigue, headache, dizziness
	Psychiatric illness
	Cataracts
	Rheumatoid arthritis
	Dyspepsia, abdominal cramping
	Permanent liver or kidney damage
	Rash
	Alopecia
	Gynecomastia
	Pseudolupus syndrome
	Weight gain

intolerance are the statin-associated muscle symptoms (SAMSs) occurring in 1% to 10% of patients.[15] Other side effects are listed in **Table 1**. The National Lipid Association Expert Panel on Statin Intolerance defines statin intolerance as a clinical syndrome characterized by the inability to tolerate at least 2 statins, 1 statin at the lowest starting daily dose (rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg) and another statin at any daily dose due to either objectionable symptoms (real or perceived) or abnormal laboratory values, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease).[15] In short, before diagnosing a case of statin intolerance, other possible etiologies should first be ruled out and different statins tried at varying doses.[14] The universal definition of statin intolerance as the inability to tolerate 2 different statins is applicable to Korean population, yet further investigations are needed to capture its incidence among them.

Although very few patients (<1%) develop serious side effects due to statins, the toxicity of these agents became of great public interest when cerivastatin was withdrawn from the market as a result of deaths from rhabdomyolysis.[13,16,17] In this regard, if the side effects still remain intolerable and/or there is over a 10-fold increase in the serum creatinine kinase (CK) level along with an increase in serum creatinine level, it is recommended to discontinue statin therapy.[13,15,18]

Mechanisms of and risk factors for statin intolerance

Stain intolerance has been reported as multifactorial and dose-related. Any condition that increases serum statin levels increases the risks of statin intolerance. Such factors include low body mass index, female sex, old age, Asian ethnicity, comorbidity (e.g., hypothyroidism, liver and kidney diseases, and rheumatic diseases), vitamin D deficiency, alcoholism, grapefruit juice consumption (1 qt/day or 0.95 L/day), major surgery or perioperative period, excessive physical activity, history of myopathy while receiving another lipid-lowering therapy, history of CK rise, family history of myopathy, and family history of myopathy while receiving another lipid lowering agent.[5,12,13,19,20] The risk is also increased with the use of

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concomitant medications such as fibrates, cyclosporine, antifungals, macrolide antibiotics, amiodarone, verapamil, and anti-HIV drug-protease inhibitors.[5,13,19,20]

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, the Heart Protection Study, and the Prediction of Muscular Risk in Observational Conditions Study showed there are genetic factors associated with statin intolerance.[20] Inconsistent association is seen with DNA polymorphism in genes that code for organic anion-transporting polypeptide 1B1, P450 isoenzymes, coenzyme Q, myophosphorylase, carnitine palmitoyl transferase II, myoadenylate deaminase, adenosine triphosphate (ATP)-binding cassette sub-family B member 1, ATP-binding cassette subfamily G member 2, the efflux transporter multidrug resistance protein and serotonin pain receptors.[19-21]

MANAGEMENT OF STATIN INTOLERANCE

When a patient on statin treatment develops symptoms of myopathy, the first step is to measure his/her serum CK level. If it is more than 10 times the upper limit of normal or the serum creatinine level is elevated, it indicates rhabdomyolysis which can be fatal. Prompt discontinuation of statin is strongly recommended, and the patient should be hydrated immediately.[19] The patient should be assessed and treated for contributing factors such as excessive physical activity, consumption of grapefruit juice, use of concomitant medications that increase statin intolerance, hypothyroidism, and vitamin D deficiency.[5]

Kajinami et al.[22] presented the web-based survey data how clinicians manage statin intolerant patients among doctor form Japan, Taiwan, and Korea (n=180). The accurate prevalence of statin intolerance is not investigated. Switching to low-dose or low potent statin treatment is frequently observed among general physicians in Korea and Taiwan compared to Japan. Non-statin lipid lowering therapy such as fish oil is commonly prescribed with low dose statin in Korea compared to other countries.[22] However, there is lack of data for the prevalence and management option in Korean situation.

Switching to another statin

Patients with high risks for CVD should be maintained on a statin-based regimen. Switching to another statin has been found to be efficacious in many patients.[5,18,19,22] Statins with low risks such as fluvastatin and pravastatin may be used even though they may not be potent enough to reduce the LDL-C to target values in some patients.

Intermittent statin dosing

Another mode of using a statin-based therapy is to reduce the dose of the medication. Long-acting statins may be given either at reduced doses or at reduced frequency (1–3 times a week).[18,23] Rosuvastatin with a half-life of 19 hours and atorvastatin with a half-life of 11–24 hours are particularly useful in this approach.

Non-statin-based lipid-lowering therapies

A non-statin therapy may be tried if the patient does not tolerate any statin or when statins used at maximal tolerable dose fail to reduce the LDL-C to the target level. The most commonly used non-statin lipid-lowering agent is ezetimibe. When used as a monotherapy or in combination with a low-risk statin, it causes a 15% to 20% decrease in LDL-C.[24] Being an intestinal agent with no systemic effects, it is not likely to worsen the myalgia. Recently, it

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has also been shown to reduce the risk of CV events.[25] Bile acid sequestrants (BAS) reduce CV events and may be tried together with ezetimibe to produce better lipid control.[24] However, BAS is often discontinued due to high (40%–60%) rates of gastrointestinal side effects.[24] Colesevelam, a BAS with fewer side effects, leads to better adherence to therapy. Fibrates primarily decrease TG and increase high-density lipoprotein cholesterol (HDL-C) levels; the decrease in LDL-C is less marked. In recent meta-analysis, fibrates failed to show clinical benefit when added on statin therapy.[24,26,27] Niacin lowers LDL-C by about 20%. Up to 25% of the patients may discontinue niacin due to its side effects such as flushing and it is rarely used in Korea. It does not show substantial CV benefits.[24,28]

Clinicians, therefore, often consider ezetimibe as the first choice for non–statin-based lipid-lowering therapy. It may be followed by a combination of BAS or fibrates with ezetimibe. But Korean doctors prescribed fish oil frequently with statins, which has no proven benefits by far.

If both the risk for CVD and the LDL-C level are high despite drug therapy at maximal tolerable doses, LDL apheresis can be tried.[29] It is used mainly for treating patients with severe dyslipidemia like FH and may be used to lower the dose of statins.

Nutraceuticals and complementary therapies

Different dietary modifications have been used to decrease LDL-C levels. These include the use of low saturated fat diets, avoidance of trans fatty acids, and the use of viscous fibers and foods with plant sterols and stanols to decrease LDL-C levels.[12,29] Though red yeast rice is used to lower LDL-C in statin-intolerant patients, its safety and efficacy have not been proved.[29] However, the European Atherosclerosis Society consensus panel believes that the portfolio diet, containing plant sterols, soya protein, viscous fibers, and nuts, can be used either alone or with pharmacologic therapies to lower LDL-C.[5] Other therapies such as ubiquinone (Coenzyme Q10 [CoQ10]) and vitamin D supplementation also improve statin tolerability but those supplementation is not essentially needed.[5,29]

NEW AGENTS APPROVED FOR REDUCING LDL-C

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The gain of function mutations for PCSK9 gene has been linked to high cholesterol levels. The most promising approach to PCSK9 inhibition is the use of monoclonal antibodies (mAbs) targeting PCSK9. The 2 PCSK9-inhibiting mAbs approved so far in the United States, Europe, and Japan are alirocumab and evolocumab.[24,30,31] Both these drugs produce a large reduction in LDL-C.[32,33]

In healthy volunteers with baseline LDL-C >100 mg/dL, just a single dose of alirocumab (50, 100, 150, and 250 mg) administered subcutaneously or intravenously reduced the LDL-C by up to 65 percentage points compared to a placebo.[34] Alirocumab, with all doses, showed similar LDL-C response irrespective of whether there was FH or non-FH and whether the patients were on atorvastatin or on diet alone within 2 weeks of maximal LDL-C lowering efficacy.[34,35]

In the ODYSSEY ALTERNATIVE randomized trial comprised of statin-intolerant patients with primary hypercholesterolemia, alirocumab induced greater LDL-C reductions than ezetimibe.[36] In the intent-to-treat population, alirocumab (75 mg or 150 mg every 2 weeks) reduced mean LDL-C level by 45% compared with 14.6% in the ezetimibe (10 mg/day) group

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(mean difference, −30.4; p<0.0001) at 24 weeks. Alirocumab group (n=52, 41.9%) achieved the LDL-C goal of <70 mg/dL or <100 mg/dL (based on the CV risk) than in the ezetimibe group (n=5, 4.4%).[36] In the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS) phase 2 trial, evolocumab was administered to 160 statin-intolerant patients.[37] Subcutaneous administration of the evolocumab was associated with dose-dependent LDL-C reductions of about 41% with 280 mg to about 51% with 350 mg and about 63% with 420 mg evolocumab plus 10 mg ezetimibe.[37] In the GAUSS-3 trial in statin-intolerant patients, in comparison to oral ezetimibe 10 mg daily, subcutaneous evolocumab 420 mg monthly reduced LDL-C to significantly lower levels after 24 weeks.[38] The Durable Effect of PCSK9 Antibody Compared with Placebo Study showed that evolocumab (420 mg every 4 weeks) reduced the LDL-C by an additional 55% to 60% in patients on background lipid-lowering therapy with diet alone or diet plus atorvastatin 10 mg daily, atorvastatin 80 mg daily, or atorvastatin 80 mg plus 10 mg ezetimibe for 4–12 weeks.[39] Long-term tolerability and adherence was also good.[39] In a large phase 3 study of alirocumab (150 mg subcutaneously every 2 weeks), involving 2,341 patients at high risk for CVD, alirocumab was added to statin therapy at the maximum tolerated dose.[40] In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects Elevated Risk study, 27,564 patients received subcutaneous evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo in addition to statin therapy.[41] PCSK9 inhibition lowered the LDL-C by 59% from a median of 92 to 30 mg/dL, and CVD risks reduced significantly.

Thus, PCSK9 inhibition with either alirocumab or evolocumab has been proven to lower LDL-C levels even in statin-intolerant patients to a greater extent than did changing over to a different statin, increasing the dose of statins, or adding ezetimibe. This new category of drugs is expected to be a potential treatment option in reducing CVD risks for statin-intolerant patients.

Lomitapide

Lomitapide is a microsomal TG transfer protein inhibitor used as an adjunct to other lipid-lowering therapies in patients with homozygous FH. It reduces LDL-C by up to 40% and can be used along with lipid apheresis for an additive effect.[42,43] However, still the concern is on the increase of hepatosteatosis in human clinical trials.

Mipomersen

Mipomersen, a second-generation antisense oligonucleotide, inhibits the synthesis of apolipoprotein B and lowers LDL-C in high-risk statin-intolerant patients. In phase 3 studies, it reduced LDL-C by up to 36% in homozygous FH.[42] It is used as an adjunct to other lipid-lowering therapies.

NEWER LIPID-LOWERING AGENTS

As there is a need for more efficacious and safe drugs for decreasing LDL-C, several other lipid-lowering agents are also evolving.

Newer therapies for the non-FH and heterozygous FH population

Several therapies are being studied for widespread use in non-FH and heterozygous FH. Newer PCSK9 inhibitors being studied for these indications include mAbs (LY3015014 and RG7652 in phase 2), the adnectin (BMS-962476, in phase 1), and the small interfering RNA (ALN-PCS/inclisiran).[44] Results from the phase 2 ORION-1 study recently showed that

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inclisiran lowered LDL-C levels in patients with high CV risk and elevated LDL-C levels.[45] Genetic mutations leading to cholesteryl ester transfer protein (CETP) deficiency are associated with increases in HDL-C. This led to speculation that CETP inhibitors may reduce the risk of CVD. CETP inhibitors in clinical development show variable effects with increases in HDL-C, varying from 35% to over 150% and LDL-C reduction being minimal to about 45%.[44] Trials with torcetrapib and dalcetrapib have been terminated as torcetrapib showed an increase in CVD events while dalcetrapib did not improve CVD events compared to placebo.[44] A phase 2 study of TA-8995 showed significant LDL-C reductions after 12 weeks on various monotherapy doses or in combination with statins and currently is being studied in a phase 3 trial.[44] Another CETP inhibitor, anacetrapib was reported to have lower incidence of major coronary events than placebo in patients with atherosclerotic vascular disease and receiving intensive statin therapy.[46] Furthermore, clinical development of evacetrapib was terminated based on the safety observations in an interim analysis.[47]

ETC-1002 is an oral agent that directly inhibits hepatic ATP citrate lyase and leads to decrease in de novo cholesterol synthesis and increased expression of LDL receptors. It reduces LDL-C by up to 30% when administered as a monotherapy, and the reduction increases up to 43% and 48% for 120 mg and 180 mg of ETC-1002 plus ezetimibe, respectively.[48]

A new niacin-related compound, CAT-2054, has been tried in healthy volunteers. It was well tolerated with no flushing reports at doses ≤500 mg/dL.[44] The drug is planned to enter phase 2 studies. Another niacin-related compound, ARI-3037MO, caused statistically significant mean decreases in renormalization groups of 56.7% and increases in HDL-C of 7.7% in healthy volunteers at a 6 g daily dose without causing flushing, itching, or other dermatological changes.[44] The extent of its effect on the LDL-C level of dyslipidemic population is yet to be determined.

NEWER THERAPIES FOR ORPHAN HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIC POPULATION

While 2 orphan drugs, lomitapide and mipomersen have recently been approved for homozygous FH, several other drugs are in the pipeline.[44] A phase 2 open-label, dose-escalation, proof-of-concept trial has been started in homozygous FH patients for the peroxisome proliferator-activated receptor agonist, MBX-8025. Gemcabene, an acetyl coenzyme A carboxylase inhibitor, demonstrated moderate LDL-C lowering and good safety in phase 1 and 2 trials for wide use in all patients. Now, it is being developed for homozygous FH and a proof-of-concept phase 2 study is planned. Another interesting target for treating hyperlipidemia is the angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 inhibitors such as REGN1500, ISIS-ANGPTL3Rx, and ALN-ANG are in various stages of preclinical and clinical studies.

CONCLUSION

Although statins are safe and effective in dyslipidemic patients, the main reason for statin nonadherence or discontinuation is the complaint of SAMS. Patient noncompliance can adversely affect the CVD benefits of statins. An optimal approach to achieve the target LDL-C levels is to switch to a low-risk statin at maximally tolerated dose or at intermittent non-daily dose and to combine it with a non-statin lipid-lowering agent and/or dietary modifications.

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The most commonly used non-statin agent is ezetimibe. Others include BAS, fish oil, CoQ10, and vitamin D supplementation.

We could use several new pharmacological agents that are approved or being studied for use in statin intolerant patients. Of these, PCSK9 inhibitors such as alirocumab, evolocumab, and MTP inhibitor: lomitapide and Apo B antisense oligonucleotide: mipomersen have recently been approved for reducing LDL-C levels.

Above all, we need our own data of the prevalence of statin-intolerant patients. The current situation of how Korean physicians manage the statin intolerance for using those new drugs properly in Korea.

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