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Gradual Increase of LDL Cholesterol Lowering Power by Pharmaceutics Medications

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Abstract

As the medications with different types of action increase in their power for low density lipoprotein cholesterol (LDL-C) lowering there it great interest in their mechanisms of action that can lead to new pharmacological interventions. Ezetimibe is an inhibitor of dietary and bile cholesterol absorption and binds to the "Niemann-Pick C1-Like 1 (NPC1L1)" protein, located in the brush border cells of the intestinal epithelium, blocking cholesterol absorption, which confers a 15% to 20% reduction in plasma cholesterol. Having established the efficacy and safety of very low LDL-C values with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors plus statins in the short and medium term, the long-term benefits were determined by the open-label extension of the FOURIER study (FOURIER-OLE). The FOURIER-OLE study also demonstrated that the earlier the reduction in LDL-C, the greater the reduction in cardiovascular risk, consistent with the legacy effect observed in trials with statins and PCSK9 inhibitors. Inclisiran is a novel small interfering RNA-based therapy administered as a twice-yearly subcutaneous injection. By binding to the messenger RNA (mRNA) precursor of PCSK9, inclisiran inhibits expression of the PCSK9 gene, resulting in increased recycling and expression of LDL receptors and decreased levels of LDL-C. Like PCSK9 inhibitors, inclisiran was associated with a comparable extent of LDL-C reduction in several phase II/III trials. In conclusion, prevention is the mainstay of atherosclerosis treatment, whether it is prevention of the onset of the atherogenic process or prevention of the progression of atherosclerotic lesions. Facilitating measures that can prevent these processes must be increasingly implemented.

Keywords: Cholesterol; Medications; ORION; Familial hypercholesteremia; Treatment

Abbreviations: LDL-C: Low Density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9

Introduction

Inhibitors of intestinal cholesterol absorption

With the evolution of lipid-lowering therapy, drugs with different mechanisms of action, such as ezetimibe, were developed. Ezetimibe is an inhibitor of dietary and biliary cholesterol absorption and binds to the "Niemann-Pick C1-Like 1 (NPC1L1)" protein, located in the brush border cells of the intestinal epithelium, blocking cholesterol absorption, which confers a 15% to 20% reduction in plasma cholesterol [1]. In the randomized IMPROVE-IT study, 18,144 individuals with acute coronary syndrome were randomized to statin treatment versus statin plus ezetimibe. In the statin plus ezetimibe group, there was an additional 16 mg/dl reduction in low-density lipoprotein cholesterol (LDL-C), with a 6.5% proportional reduction in major cardiovascular events at 5 years [2].

Benefits in further lowering LDL-C in very high-risk populations have been demonstrated and that more aggressive targets are needed to reduce residual risk. In this context, the Sharp study evaluated 9,270 individuals with chronic kidney disease and compared the association of simvastatin and ezetimibe versus placebo. The mean reduction in LDL-C levels was 33 mg/dl with the combination treatment compared to placebo, resulting in a lower incidence of major cardiovascular events, conferring a continuous risk reduction [3]. These data are in agreement with genetic data from randomized trials, demonstrating that variants

in the 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and NPC1L1 genes have biologically equivalent effects on cardiovascular disease risk, per unit of LDL-C reduction [4]. Treatment with statins and ezetimibe, which are low-cost oral therapies, has been widely used in patients at high risk and with more aggressive LDL-C reduction targets.

Adverse effects of statins

The efficacy of statins in reducing major cardiovascular events in secondary prevention is well established, with a highly favorable benefit/risk profile. In primary prevention, evidence of benefit is less robust, due to the low incidence of events in this population, giving rise to a debatable relationship between benefit and risk. In this context, the document "Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association", a 2019 publication, makes some recommendations on safety and prevalence of adverse events related to statins [5].

a) Statins may cause dose-related myopathy, defined as muscle pain without clear etiology or weakness accompanied by CK elevations > 10 times the normal value, including rhabdomyolysis, occurring in < 0.1% of patients. The risk of myopathy and rhabdomyolysis is related to circulating concentrations of active drugs, which interfere with statin metabolism. There is a growing appreciation and expectation of statins as a cause of muscle damage in treated patients, conveyed by negative information in the media. Such symptoms should never be ruled out by the clinician. Although muscle symptoms are very unlikely to be caused by statins, repeat treatment with the same statin at lower doses or another statin is useful in resuming treatment (when myopathy is excluded) as it reduces the risk of cardiovascular events, particularly in high-risk patients, including those with pre-existing coronary artery disease.

b) Statins may cause asymptomatic (dose-related) transaminase elevations above three times the normal value in approximately 1% of patients, but this alone does not indicate liver injury. Transaminase monitoring is not useful for preventing clinically statin-related hepatotoxicity, which is extremely rare, occurring in approximately 0.001%. It is not possible to predict which patients will develop severe hepatotoxicity, hence the recommendation to monitor for symptoms and warning signs in patients with preexisting liver disease.

c) Statins modestly increase the risk of developing diabetes mellitus by unidentified mechanisms, with increased risk associated with high doses. The risk is higher in patients with multiple pre-existing risk factors for diabetes mellitus. The absolute risk of statin-induced diabetes mellitus in pivotal trials was approximately 0.2% per year. The extent of any effect in routine clinical practice will depend on the initial risk of developing diabetes mellitus in patients. In the diabetic population, the mean increase in glycated hemoglobin (HbA1c) with initiation of statin therapy is small with limited clinical significance. Statin therapy substantially reduces the risk of cardiovascular events in individuals with and without diabetes mellitus and that more cardiovascular events are prevented for each new diagnosis of diabetes mellitus.

d) Statins do not increase the risk of cerebral hemorrhage in patients in the primary prevention of stroke. An increased risk is possible in secondary stroke prevention populations, but the absolute risk is very small and the benefit in reducing overall stroke and other vascular events outweighs the risk.

e) Statins such as rosuvastatin at a maximum dose of 40 mg may cause transient proteinuria and microscopic haematuria, but in the long term, including rosuvastatin, there is no worsening of proteinuria in the long term nor worsening of renal function. However, in the setting of cardiac surgery, perioperative treatment with statins in statin-naïve patients may increase the risk of kidney injury.

The summary of the above recommendations is based on numerous observational studies, registries, randomized studies, among others, in more than 30 years of clinical investigation, demonstrating that statins have few serious adverse effects. With the exception of hemorrhagic stroke, the possible cause of newly diagnosed diabetes mellitus, and a few rare cases of autoimmune necrotizing myositis, the adverse effects of statins can almost always be reversed by stopping treatment. In contrast, acute myocardial infarction or ischemic stroke permanently damage an individual's heart or brain, and can even be fatal. In the patient population for whom statins are recommended by current guidelines, the benefit of cardiovascular risk reduction far outweighs the adverse effects.

Long-term efficacy and safety of very low LDL-C values

Having established the efficacy and safety of very low LDL-C values with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors associated with statins in the short and medium term, the long-term benefits were determined by the open-label extension of the FOURIER (FOURIER-OLE) study [6]. This study covered a portion of the patients originally included in the FOURIER study, which originally included about 27,000 patients, of whom 6,635,000 participated in the extension. Regardless of treatment in the original study, all patients converged on evolocumab at a dose of 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly. The maximum exposure to evolocumab in the original FOURIER plus FOURIER-OLE study was 8.4 years (median 7.1 years). After 12 weeks on the FOURIER-OLE diet, the median LDL-C was 30 mg/dl. The results demonstrated that patients originally assigned in the original study to receive evolocumab versus placebo in the extension phase had a 15% lower risk of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, HR. 0.85 [95% CI, 0.75-0.96]; P = 0.008), 20% lower risk of cardiovascular death, myocardial infarction, or stroke (HR 0.80 [0.68-0.93]; P = 0.003), and a 23% lower risk of cardiovascular death (HR 0.77 [0.60-0.99]; P = 0.04).

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The reduction in cardiovascular mortality was not observed in the original FOURIER study, perhaps due to the short duration (2.2 years), but was evident in the long-term extension.

Given that the reduction in major adverse cardiovascular events increases with prolonged exposure to low LDL-C levels, it is possible that reduced mortality may also have followed this path. There were no significant differences in the incidence of serious adverse events, including myopathy, incidence of diabetes, hemorrhagic stroke, and neurocognitive events between the two treatment arms [6]. This study demonstrated that long-term LDL-C reduction with evolocumab was safe and well tolerated for a median of 7.1, with additional benefits on cardiovascular outcomes in both high- and very high-risk populations [6]. These results contributed to establishing the safety and tolerability of prolonged and pronounced LDL-C reduction, and validated the evidence that the lower the LDL-C values and for a prolonged time, the greater the benefit of risk reduction. The FOURIER-OLE study also demonstrated that the earlier the reduction in LDL-C, the greater the reduction in cardiovascular risk, consistent with the legacy effect observed in statin trials [7,8]. Just as statins provide some degree of protection against the risk of atherosclerotic disease even after discontinuation of therapy, early initiation of PCSK9 inhibitors attenuates the risk, which is not seen when therapy is delayed. These data together confirm that it is LDL-C lowering, and not a specific class of lipid-lowering therapy, that drives cardiovascular benefit [9].

Although participants in the FOURIER-OLE study benefited from the addition of the PCSK9 inhibitor, and earlier initiation of this therapy was associated with greater benefits, event rates in both groups remained high. When considering only the FOURIER-OLE study, which compares two groups in the current best lipid-lowering regimen, with a 2-year interval between one arm and the other, the cumulative incidence of the primary composite endpoint was 17.5% in those initially assigned to placebo and 15.4% in those initially assigned to evolocumab, in the original study. Despite therapeutic advances in reducing LDL-C levels, the percentage of patients who achieve adequate reduction is still small, leaving this population susceptible to the progression of atherosclerosis and acute cardiovascular events. The FOURIER-OLE data provide an additional justification for intensifying efforts in reducing cardiovascular risk [10,11].

What the guidelines recommend

The benefit of intense LDL-C reductions, especially in high or very high risk populations, opens the prospect for a paradigm shift, where the concept of high doses of potent statins is modified by high-intensity lipid-lowering treatment. The challenge is how to implement this strategy, considering that in order to achieve increasingly aggressive goals, it will be necessary to associate drugs other than statins, such as ezetimibe, PCSK9 inhibitors (monoclonal antibodies or inclisiran) and bempedoic acid (cholesterol synthesis inhibitor, complementary to statins) [1]. In this context, the risk stratification of the patient is fundamental, since the risk reduction is a function of the absolute reduction of LDL-C. Based on the risk, it is evaluated how aggressive the prescription will be to achieve the recommended goals. The 2019 European Guideline, for example, considers for high-risk patients, a target LDL-C < 70 mg/dl and a reduction > 50% from baseline; for very high risk, a target LDL-C < 55 mg/dl and a reduction > 50% from baseline; and for patients with acute coronary syndrome, within a two-year period, a target LDL < 40 mg/dl [12]. In order to achieve these more aggressive goals, the combination of drugs is necessary, especially in patients with eligibility criteria for new lipid-lowering drugs, in addition to adequate clinical judgment.

1.1.1.Inclisiran: inclisiran is a novel small interfering RNA-based therapy administered as a twice-yearly subcutaneous injection. By binding to the messenger RNA (mRNA) precursor of PCSK9, inclisiran inhibits expression of the PCSK9 gene, resulting in increased recycling and expression of LDL receptors and decreased levels of LDL-C. Like PCSK9 inhibitors, inclisiran was associated with a comparable extent of LDL-C reduction in several phase II/III trials. Compared with placebo, inclisiran was found to have similar adverse events except for injection-site reaction [13-17].

Conclusion

Atherosclerosis causes many other diseases in addition to coronary artery and cerebrovascular disease, including dementia, peripheral artery disease, heart failure, renal artery stenosis, carotid artery stenosis and embolization, kidney failure, aortic disease, mesenteric artery disease, erectile dysfunction, frailty, and premature aging. The “burden” of this disease is reflected by its systemic, debilitating, disabling and sometimes deadly character. Therefore, the importance of increasing efforts in prevention and treatment is justified [18].

The relationship between hypercholesterolemia and atherosclerosis took root more than 100 years ago. Advances have provided a more granular and extensive understanding of atherogenesis, and how elevated LDL-C is a causal and crucial factor in this process. There has been an exponential growth of scientific tools and methods that have accelerated the understanding of the complex mechanisms that result in atherosclerosis and its consequences [18]. Evidence from randomized studies with statins alone or associated with ezetimibe was overwhelming in pointing to the benefits of LDL-C reduction in primary and secondary prevention.

Studies with PCSK9 inhibitors associated with conventional statin therapy, in high- or very high-risk patients, demonstrated that additional reductions in LDL-C, even at values below 20 mg/dl, impacted benefits on cardiovascular outcomes, with no evidence of harm. These data converge with Mendelian randomization studies, in which patients with lower LDL-C values, from birth, do not have atherosclerosis [18]. Currently, the discussion seems to be about the early reduction of LDL-C values, before the beginning of the atherogenic process, since there is a

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therapeutic arsenal that could meet these demands, but there is still no evidence of how early these interventions should occur. Even with guidelines, risk stratification tools, and algorithms for the eligibility of patients who benefit from more aggressive LDL-C targets, few patients at high risk or in secondary prevention are in the recommended treatment targets. And in primary prevention, this scenario is less promising. Therefore, prevention is the basis of the treatment of atherosclerosis, whether it is the prevention of the onset of the atherogenic process or prevention of the progression of atherosclerotic lesions. Facilitating measures that can prevent these processes must be increasingly implemented.

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