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STATIN DURATION AND CARDIOVASCULAR RISK REDUCTION

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Abstract:

Hyperlipidemia is one of the leading risk factors for the development of cardiovascular diseases (CVD). According to European and Russian guidelines, first-line drugs for the treatment of hyperlipidemia that have demonstrated their effectiveness in reducing cardiovascular morbidity and mortality are statins. Prescribing adequate lipid-lowering therapy helps slow the progression of atherosclerosis and, as a consequence, prevent the development of CVD, patient disability, as well as reduce the frequency of re-hospitalizations for the purpose of myocardial revascularization, however, the success of statin use largely depends on the patient's adherence to treatment. One of the most effective, studied, prescribed and sold drugs of this class is atorvastatin. This paper provides an overview of clinical studies of the effectiveness of atorvastatin. Numerous large-scale clinical trials (GREACE, TNT, MIRACL, AVERT, etc.) have shown the effectiveness of the original atorvastatin in the primary and secondary prevention of CVD. Aspects of the use of atorvastatin in comorbid patients with diabetes mellitus, arterial hypertension, chronic kidney disease, and acute cerebrovascular accident are considered. The authors also provide data from current safety studies of atorvastatin, in which the original atorvastatin convincingly demonstrates safety and good tolerability in doses ranging from 10 to 80 mg.

Keywords

Statins, hyperlipidemia, cardiovascular diseases, cardiovascular risk.

Introduction

Cardiovascular diseases (CVDs) continue to be the leading cause of death worldwide. Thus, in the Russian Federation, mortality from CVD in 2022 was 587.6 cases per 100 thousand population with the initial registration of 4 million 706 thousand patients with diseases of the circulatory system [1].

The global burden of obesity, diabetes mellitus (DM), metabolic syndrome and hyperlipidemia is constantly increasing and may become the largest known non-infectious pandemic, which will subsequently lead to a huge increase in atherosclerotic CVD. The development of CVD largely depends on modifiable risk factors, but in clinical practice

often insufficient efforts are made to normalize body weight, correct blood glucose levels, and low-density lipoprotein cholesterol (LDL-C) levels. Hyperlipidemia is one of the leading risk factors for the development of CVD. According to European and Russian guidelines, first-line drugs for the treatment of hyperlipidemia that have demonstrated their effectiveness in reducing cardiovascular morbidity and mortality are statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMG-CoA reductase] inhibitors) [2, 3]. Prescribing adequate lipid-lowering therapy helps slow the progression of atherosclerosis and, as a consequence, prevent the development of CVD, patient disability, as well as reduce the frequency of re-hospitalizations for the purpose of myocardial revascularization, however, the success of statin use largely depends on the patient's adherence to treatment. Atorvastatin (Liprimar) is a synthetic drug from the statin group, approved by the U.S. Food and Drug Administration in 1996. It is one of the most effective, studied, prescribed and sold drugs of this class. Atorvastatin competitively inhibits HMG-CoA reductase, which converts 3-hydroxy-3-methylglutaryl-CoA to mevalonate, and thereby reduces cholesterol production in the liver. In addition, atorvastatin also increases the number of LDL cholesterol receptors on the surface of liver cells. Atorvastatin is approved for the treatment of adults with primary hyperlipidemia (heterozygous familial and non-familial), mixed dyslipidemia, hypertriglyceridemia, primary dysbetalipoproteinemia, homozygous familial hypercholesterolemia, as well as in children with heterozygous familial hypercholesterolemia , if it is impossible to achieve target values of LDL cholesterol due to diet [4]. In patients with homozygous and heterozygous hypercholesterolemia, mixed dyslipidemia, isolated hypertriglyceridemia and non-familial hypercholesterolemia, this member of the statin class reduces the levels of total cholesterol, LDL cholesterol, apolipoprotein, very low-density lipoprotein cholesterol and triglycerides while increasing the level of high-density lipoprotein cholesterol. In patients with dysbetalipoproteinemia, atorvastatin reduces intermediate-density lipoprotein cholesterol levels. Numerous large-scale clinical trials (GREACE, TNT, MIRACL, AVERT, etc.) have repeatedly demonstrated the effectiveness of the original atorvastatin in the primary and secondary prevention of CVD [5–8]. Thus, atorvastatin is used for primary prevention in patients without coronary artery disease (CHD), as well as in patients with type 2 diabetes mellitus (DM) without CHD, but with several risk factors for developing CVD, to reduce the risk of myocardial infarction (MI), stroke, angina pectoris and surgical treatment of coronary artery disease. This drug is indicated in patients with coronary artery disease as secondary prevention to prevent non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalizations for congestive heart failure and angina pectoris [4]. According to current recommendations, atorvastatin therapy should be continued indefinitely in patients. Titration of drug doses is carried out until target LDL cholesterol levels are achieved, provided there are no side effects. Current guidelines suggest moderate-intensity (10–20 mg) or high-intensity (40–80 mg) atorvastatin therapy, depending on the patient's cardiovascular risk [2, 3, 9]. Thus, moderate-intensity statins should reduce LDL cholesterol levels by about 30-50%, while high-intensity doses should

reduce LDL cholesterol levels by more than 50%. A decrease in LDL cholesterol levels by 1 mmol/L is accompanied by a reduction in the risk of cardiovascular events by approximately 20%, and further reductions in cholesterol levels with more intensive regimens lead to an even more pronounced reduction in the risk of developing CVD [10]. If target LDL cholesterol levels are not achieved, patients are advised to add new lipid-lowering drugs to therapy, such as ezetimibe, inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSN9), which in a relatively short time reduce the risk of developing cardiovascular disease. vascular events [11, 12].

Use of atorvastatin in patients with coronary heart disease and acute coronary syndrome

The randomized GREACE trial in patients with documented coronary artery disease demonstrated the ability of escalating doses of atorvastatin (from 10 to 80 mg, mean dose 24 mg) to reduce total and cardiovascular mortality by 43% (p=0.002) and 47% (p=0. 0017) respectively. Taking atorvastatin was accompanied by a reduction in the incidence of cardiovascular events (MI, unstable angina, repeated myocardial revascularization) by 54% (p<0.0001) and cerebral strokes by 47% (p=0.034) [5]. In a double-blind randomized study TNT (Treating to New Target) in patients with documented coronary artery disease (n=10001) evaluated the effectiveness of different doses of atorvastatin (10 and 80 mg). Thus, on therapy with atorvastatin 80 mg, the primary endpoint (cardiovascular death, non-fatal MI, cardiac arrest with resuscitation, stroke) was identified in 8.7% of patients, and on therapy with atorvastatin 10 mg - in 10.9%. In summary, patients receiving atorvastatin 80 mg had a 22% lower risk of major events than patients receiving atorvastatin 10 mg (odds ratio (OR) 0.78, 95% confidence interval (CI) 0.69–0 .89, p<0.001) [6, 13]. The ability of high doses of atorvastatin 80 mg to reduce the incidence of ischemic events compared with endovascular treatment was shown in the AVERT (Atorvastatin Versus Revasculatization Treatment) study in 341 patients with stable coronary artery disease. Patients treated with atorvastatin 80 mg for 18 months had a 36% lower incidence of ischemic events than patients on standard therapy who underwent percutaneous coronary intervention (PCI) (p=0.048). Thus, aggressive statin therapy may be as effective as endovascular treatment in reducing the incidence of ischemic events in patients with coronary artery disease [8]. The effectiveness of the original atorvastatin at a dose of 80 mg as secondary prevention of CVD was also evaluated in patients with acute coronary syndrome (OKS). Thus, in the randomized, double-blind MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study of 3086 patients with ACS (unstable angina or acute non-ST segment elevation MI), the primary endpoint (death, non-fatal MI, cardiac arrest with resuscitation, or resumption of episodes of myocardial ischemia requiring readmission) was achieved in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group (RR 0.84, 95% CI 0.70–1.00 , p=0.048). There was also a lower incidence of symptomatic myocardial ischemia requiring emergency readmission in the atorvastatin group compared with placebo (6.2% vs. 8.4%, p=0.02) [7]. In 171 patients with ACS in the ARMYDA-ACS (Atorvastatin Pretreatment

Improves Outcomes in Patients With Acute Coronary Syndromes Undergoing Early Percutaneous Coronary Intervention) study, atorvastatin reduced the risk of 30-day cardiovascular events after endovascular treatment by 88% compared with the group placebo (in the case of atorvastatin therapy 12 hours before endovascular intervention with 40 mg perioperative) (OR 0.12, 95% CI 0.05–0.50, p = 0.004) [14]. In another trial, PROVE IT- TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 Investigators) assessed the effectiveness of atorvastatin 80 mg and pravastatin 40 mg in 4162 patients who underwent PCI due to the development of ACS. Compared with pravastatin 40 mg, atorvastatin 80 mg was associated with a reduction in the composite endpoint of death, MI, stroke, unstable angina leading to hospitalization, and revascularization within 30 days of endovascular treatment (21.5% vs. 26.5%, OR 0.78, 95% CI 0.67–0.91, p=0.002), as well as rates of infarction-related revascularization (11.4% vs. 15.4%, p=0.001) and non-infarction -connected arteries (8.0% vs. 10.5%, p=0.017) [15]. Based on this study, it was concluded that atorvastatin therapy reduces the incidence of major adverse cardiovascular events in patients with ACS undergoing PCI.

The use of atorvastatin in patients with diabetes, hypertension, chronic kidney disease, acute cerebrovascular accident

The effectiveness of the original atorvastatin has been proven in patients with concomitant diseases such as diabetes, arterial hypertension (AH) and chronic kidney disease (CKD), as well as with acute cerebrovascular accidents. The multicenter randomized trial CARDS (Collaborative AtovRastatin Diabetes Study) assessed the effectiveness of atorvastatin 10 mg for primary prevention of CVD in patients with type 2 diabetes (n=2838). At baseline, the patients had no documented CVD; the LDL cholesterol level was 4.14 mmol/l or less. Therapy with atorvastatin 10 mg was accompanied by a significant reduction in the risk of cardiac events such as death, MI, cardiac arrest with successful resuscitation, unstable angina, etc., compared with the same risk in the placebo group (5.8% versus 9.0%, p=0.001). The incidence of cerebral strokes and acute coronary events also decreased in the atorvastatin group by 48% and 36%, respectively [16]. One of the complications of diabetes is diabetic nephropathy, a disease leading to impaired renal function and the development of renal failure. Taking into account the renoprotective effect of statins [17], the effect of the original atorvastatin on renal function in patients with CKD was studied. Thus, in the CARDS study, CKD was initially detected in 34% of patients (n = 970), of which 482 patients were included in the original atorvastatin group in dose of 10 mg, the rest - in the placebo group. Taking atorvastatin at a dose of 10 mg was associated with an increase in glomerular filtration rate (GFR) by an average of 0.18 ml / min / 1.73 m2 per year (95% CI 0.04–0.32, p = 0.01) and decreased the rate of decline in GFR by 0.38 ml/min/1.73 m2 per year in patients with baseline albuminuria (95% CI 0.04–0.72, p=0.03) [18]. Also, an increase in GFR and creatinine clearance was observed during atorvastatin therapy in the GREACE and TNT studies [5, 6]. The efficacy and safety of the use of the original atorvastatin in patients with initial moderate proteinuria and hypercholesterolemia was assessed in the PLANET I study, which included patients with type 1 and 2 diabetes

(n=325), and the PLANET II study, which included 220 people without diabetes. The criterion for proteinuria was the ratio "urine protein/urine creatinine" of 500/5000 mg/g. Atorvastatin therapy was associated with a 13% decrease in proteinuria from baseline (p=0.033) in the PLANET I study, but no diagnostically significant change in GFR values was recorded (-1.61 ml/min/1.73 m2, p=0.21) . A similar picture was observed in the PLANET II study. There was a 24% decrease in proteinuria (p=0.0026) during atorvastatin therapy, while the GFR value also did not change significantly (-1.74 ml/min/1.73 m2, p=0.28). In 2022, combined data from the two studies were published. Atorvastatin therapy contributed to a decrease in proteinuria levels by 18% from baseline (p=0.0003), but no diagnostically significant change in GFR levels was detected (-1.67 ml/min/1.73 m2, p=0.097). According to a post hoc analysis of the PLANET I study, the effect of atorvastatin on GFR was analyzed based on the determination of cystatin C levels. Thus, according to the study results, there was no diagnostically significant decrease in GFR levels (-0.9 ml / min / 1.73 m2, p = 0 ,69). The data obtained demonstrated the possibility of safe use of atorvastatin in patients with diabetes and CKD [19]. In another study, ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm), which included 10,305 patients, atorvastatin demonstrated the ability to prevent the development of coronary artery disease in patients with hypertension and total cholesterol levels ≤6.5 mmol/L. Cardiovascular events, such as nonfatal myocardial infarction and death from coronary artery disease, were detected in 1.9% of patients in the original atorvastatin group and in 3.0% in the original atorvastatin group placebo group. Atorvastatin therapy contributed to a reduction in overall mortality by 13.0%, the incidence of stroke by 27.0%, and the need for endovascular treatment by 21.0% [20]. Given the statistically significant results in patients receiving atorvastatin, this part of the study was completed ahead of schedule [21, 22]. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial also demonstrated high efficacy of atorvastatin 80 mg in the prevention of recurrent ischemic stroke (primary endpoint). In addition to cerebrovascular events, cardiovascular events (secondary endpoint) were also assessed in included patients. During therapy with the original atorvastatin 80 mg, a significant reduction in the frequency of both coronary and cerebral events was revealed compared with this indicator during the use of placebo (11.2% versus 13.1%, p = 0.03; 14.1 % versus 17.2%, p=0.002, respectively). At the same time, the risk of developing cerebrovascular events decreased by 16%, and coronary events by 20% [23, 24]. In addition, a post hoc analysis of the SPARCL trial demonstrated a beneficial effect of atorvastatin in reducing the progression of CKD. Of the 1600 patients included, 789 received atorvastatin therapy at a dose of 80 mg/day. This group of patients showed a statistically significant increase in GFR compared to GFR in the placebo group (4.24±0.60 ml/min/1.73 m2 versus 2.53±0.60 ml/min/1.73 m2, respectively, p=0.008) [25].

Conclusion

Currently, three main statins are used in clinical practice: atorvastatin, rosuvastatin, pitavastatin. However, only the first two drugs can be used for high-intensity statin therapy. Each has strengths that the clinician must be aware of to optimally achieve target LDL cholesterol levels. Thus, for pitavastatin this is high safety, but a moderate lipid-lowering effect. For rosuvastatin, this is a higher incidence of achieving target LDL levels compared to other statins. For atorvastatin, this is a beneficial effect on proteinuria and the greatest study, which is true in relation to the original drug. This publication uses the results of clinical studies conducted by Pfizer from previously published original articles.

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